INDIVIDUALLY DESIGNED OPTIMUM DOSING STRATEGIES

Version: 2.9
User Manual

Table of Contents

Introduction

Individually Designed Optimum Dosing Strategies (ID – ODS™; http://www.optimum-dosing-strategies.org/) is a therapeutic drug monitoring and simulation tool powered by the R® software (version 3.3.0; Institute for Statistics and Mathematics [http://www.r-project.org/]). Based on patient demographic information readily available at the bedside, ID – ODS™ incorporates Monte Carlo simulation and inverse Bayesian modeling into the design of personalized dosing regimens. Drug concentration-time profiles are simulated using Monte Carlo simulation and inverse modeling based on linear 1 and 2-compartment intravenous or oral infusion models written in the R® language using the published, validated population pharmacokinetic parameter values and respective inter-individual variability.

Citing ID-ODS™

App: ID-ODS™. (2017). Optimum Dosing Strategies (Version 0.1.18/9500) [Mobile application software]. Retrieved from https://play.google.com/

Desktop: ID-ODS™. (2017) Optimum Dosing Strategies (Version 1.3.0) Retrieved June 02, 2017, from http://www.optimum-dosing-strategies.org/

Web: in text of document as: http://www.optimum-dosing-strategies.org/id-ods/

ID-ODS Disclaimer

We try to keep Optimum Dosing Strategies up, bug-free, and safe, but you use it at your own risk. We are providing Optimum Dosing Strategies on an "as is" basis. The Optimum Dosing Strategies Team makes no express or implied warranty of any kind with regard to this material, including, but not limited to, the merchantability, fitness for a particular purpose, and non-infringement. We do not guarantee that the services on this website will always be safe, secure or error-free or that this website will always function without disruptions, delays or imperfections. The Optimum Dosing Strategies Team shall not be liable for errors contained herein nor for possible damages in connection with the furnishing or use of this material. The Optimum Dosing Strategies Team will not be liable to any user for any lost profits or other consequential, special, indirect, or incidental, medical or non-medical damages arising out of or in connection with the use of the website, even if the Optimum Dosing Strategies Team has advised of the possibility of any such damages. Applicable law may not allow the limitation or exclusion of liability or incidental or consequential damages. In such cases, the Optimum Dosing Strategies Team's liability will be limited to the fullest extent permitted by applicable law.

All persons using the information provided here must rely on their own best professional judgment in prescribing any dosage regimen whether based on this website or not. All information provided here must always be carefully assessed and compared with the patient's clinical picture.

By using or accessing Optimum Dosing Strategies, you agree that the Optimum Dosing Strategies Team can collect and use such content and information in accordance with applicable personal data privacy laws.

System Requirements and Installation

Individually Designed Optimum Dosing Strategies (ID-ODS™) is available in a number of different channels, and more to come.

The Android mobile app is distributed via the Google Play Store at https://play.google.com/store/apps/details?id=com.idods.adult and can be installed on any Android device starting from Android version 2.1, so available on any modern Android phone or tablet (purchased after 2010).

Our desktop application can run on any recent 32- or 64-bit Windows or Linux operating system, and is available to download from the ID-ODS™ website. Mac support is available on demand. Please make sure to review the short installation guide posted on the website.

The Web Application runs in our hosted environment and accessible from mobile or desktop devices via any standard web browser and is available from the app.id-ods.org site. **Google Chrome or Mozilla Firefox with HTML5 and CSS3 support are recommended. THIS IS GREAT FOR iOS users!**

The platform is also available as a service, via a HTTPS API, so can be integrated in any online application as a back-end. On-site installation on a Linux box or as a Docker container is also available on request.

Getting Help and Updates

The Android Mobile Application is distributed via the Google Play Store, which also handles version updates and deployment as per customer settings. This means that the most recent version of the app will be downloaded and installed on the devices automatically after new releases or as per user configuration (eg. updates can be automatically installed or just downloaded).

The web application is updated by the ID-ODS™ team in our hosted environment, so thus always runs the most recent version of the ID-ODS™ platform.

You can install the most recent version of the desktop application from our homepage. Please subscribe to our newsletters to get notified about new versions.

On-site installation updates are available as per support plan.

ID-ODS™ Components

Monte Carlo Simulation

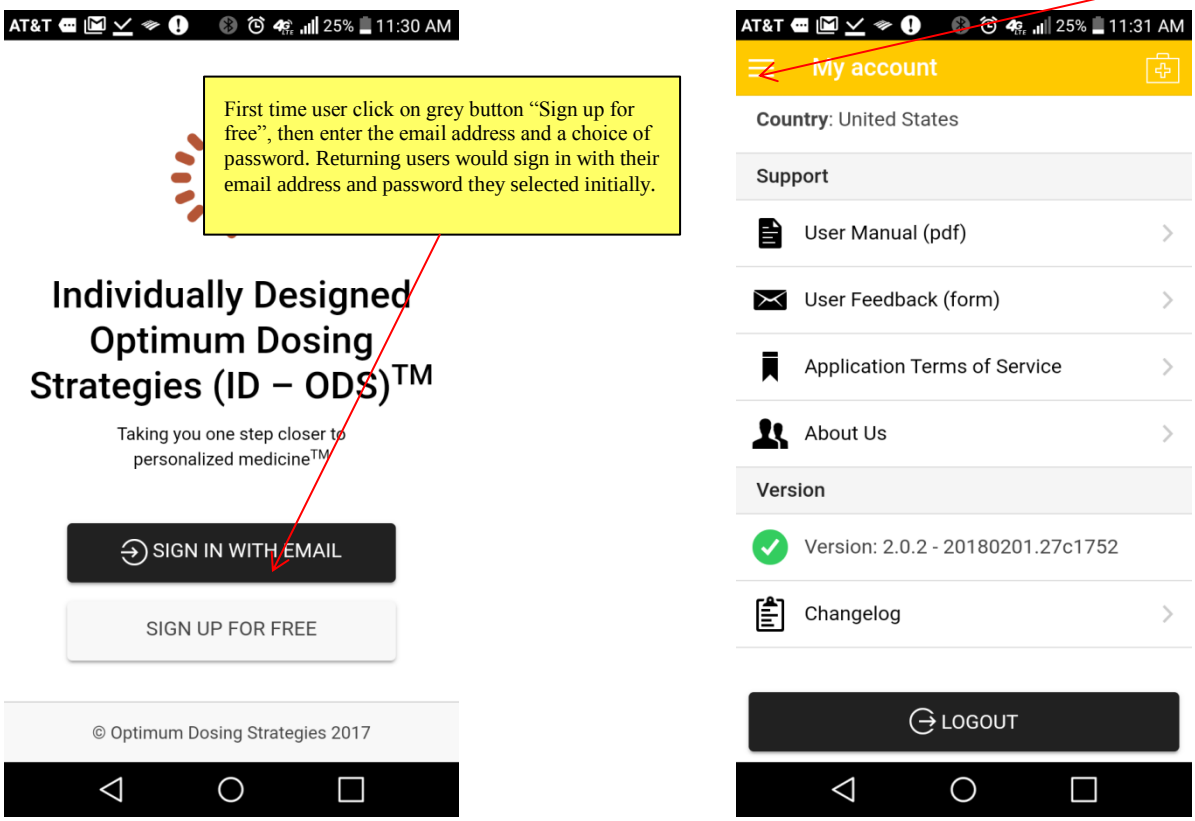
A Monte Carlo simulation is a mathematical model developed in the early 1940s to produce scenarios that require the generation of random numbers. It has many applications in physics, finance and business, and artificial intelligence. In the setting of antibiotic therapy, Monte Carlo simulations can combine pharmacokinetic and microbiological data to predict the likelihood an antimicrobial regimen will achieve a therapeutic target. This is called the probability of target attainment (PTA) where the target to be achieved is an optimal pharmacodynamic parameter for bacterial killing when considering only MICs of single values versus it is called Cumulative Fraction of Response (CFR) when considering an entire population of microorganisms. This technique is often useful in instances where the option of therapeutic drug monitoring is not available for certain antimicrobial agent.

Inverse Bayesian modeling

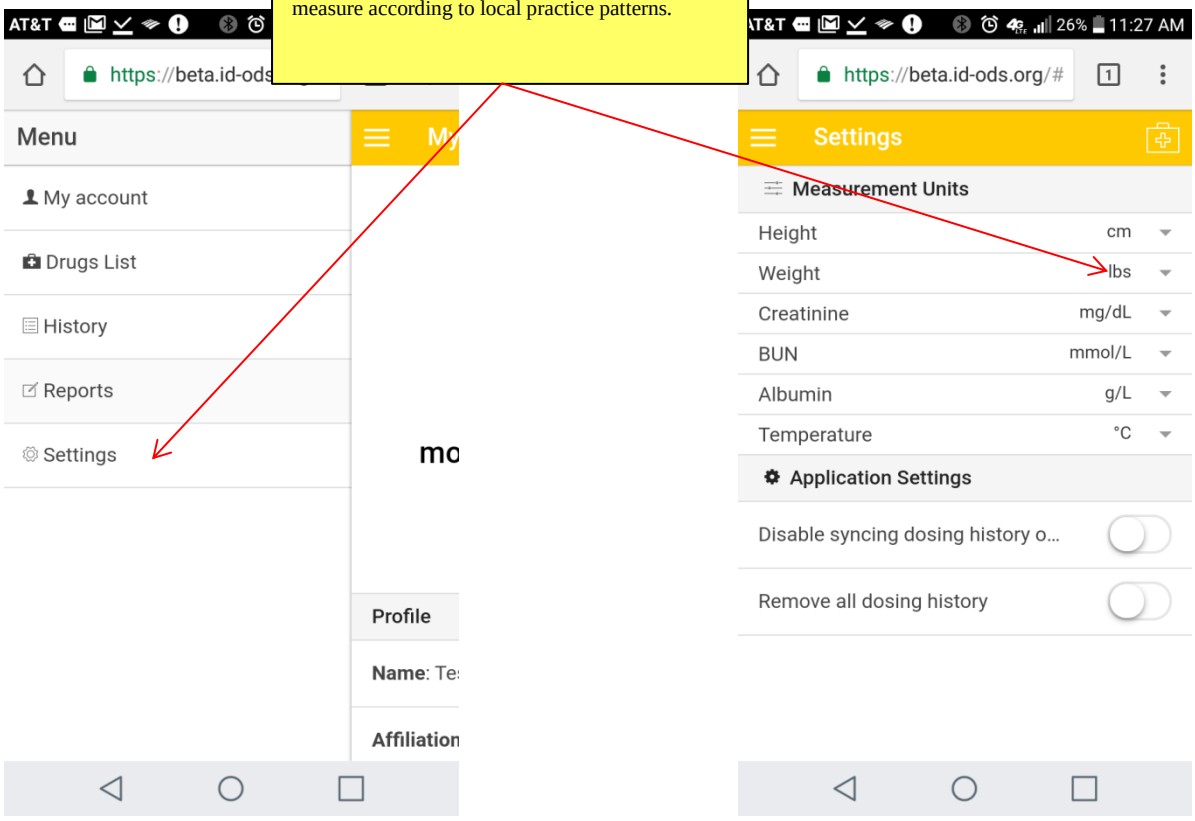
The selection of antibiotic dosage regimen in the absence of measured concentrations (ie., a priori dosing) is based on estimates of the patient's pharmacokinetic parameters adjusted for patient covariates or known demographics (ie., weight, age, sex, serum creatinine). During inverse modelling, the use of measured drug levels (ie. a posteriori dosing) is to estimate the patient's pharmacokinetic parameters from the measured antibiotic concentrations with relying on the population model. This Bayesian approach incorporates both sets of data (ie: the actual measured concentration and the population pharmacokinetic model) for estimating the patient specific pharmacokinetic parameters. It uses the a priori pharmacokinetic parameters of the population model as some starting estimate for the patient; it then adjusts these estimates based on the patient's measured antibiotic levels, taking into consideration the inter-individual variability of the population parameters and the variability of the serum level measurement. During the procedure, the serum level data is interpreted by incorporating both the variability of the population model and the variability of the serum level measurement itself. Bayes' theorem tells us quantitatively just how important every piece of information is, however it is not always able to tell whether a piece of information is relevant to the actual patient care.

First time users sign up to the app and general settings options

Once logged in, the user profile will show. To access general settings (units of measures, history settings, etc) the user should click on the small accordion here shown by the red arrow.

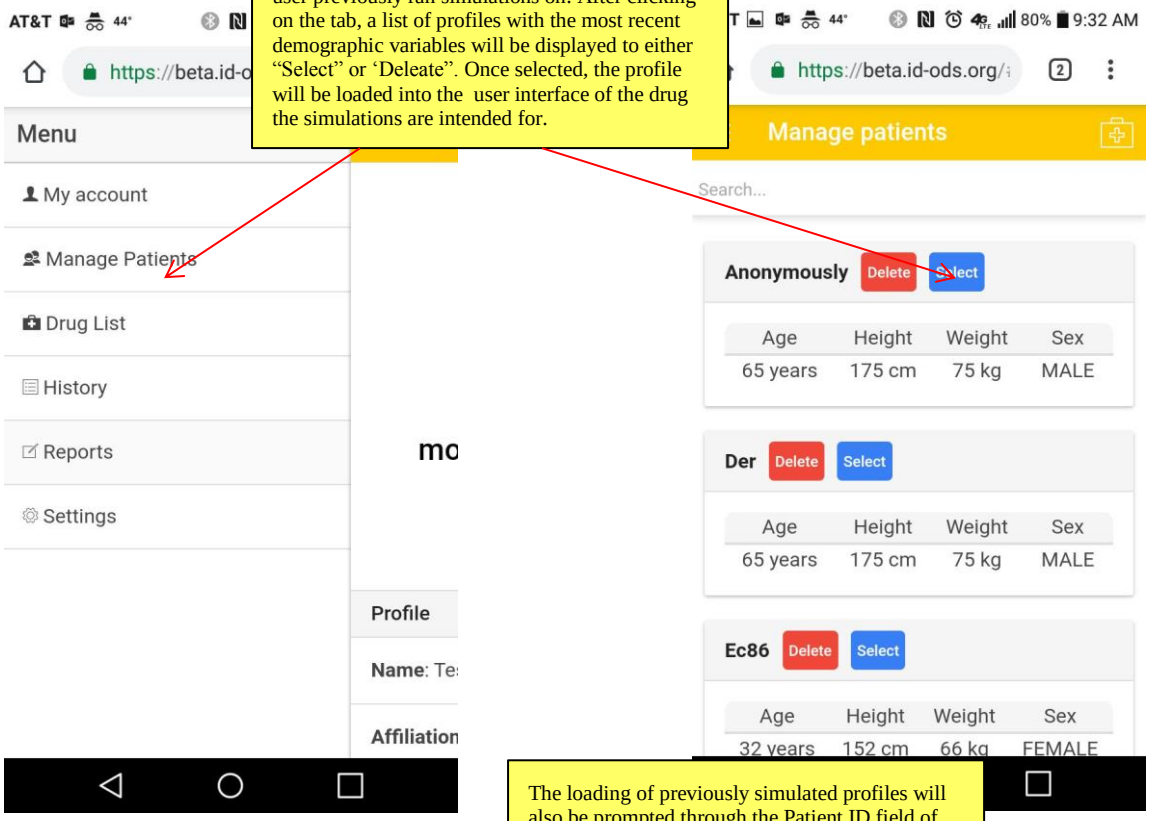


Next step to review settings just click on "Settings". Then select the preferences for units of measure according to local practice patterns.

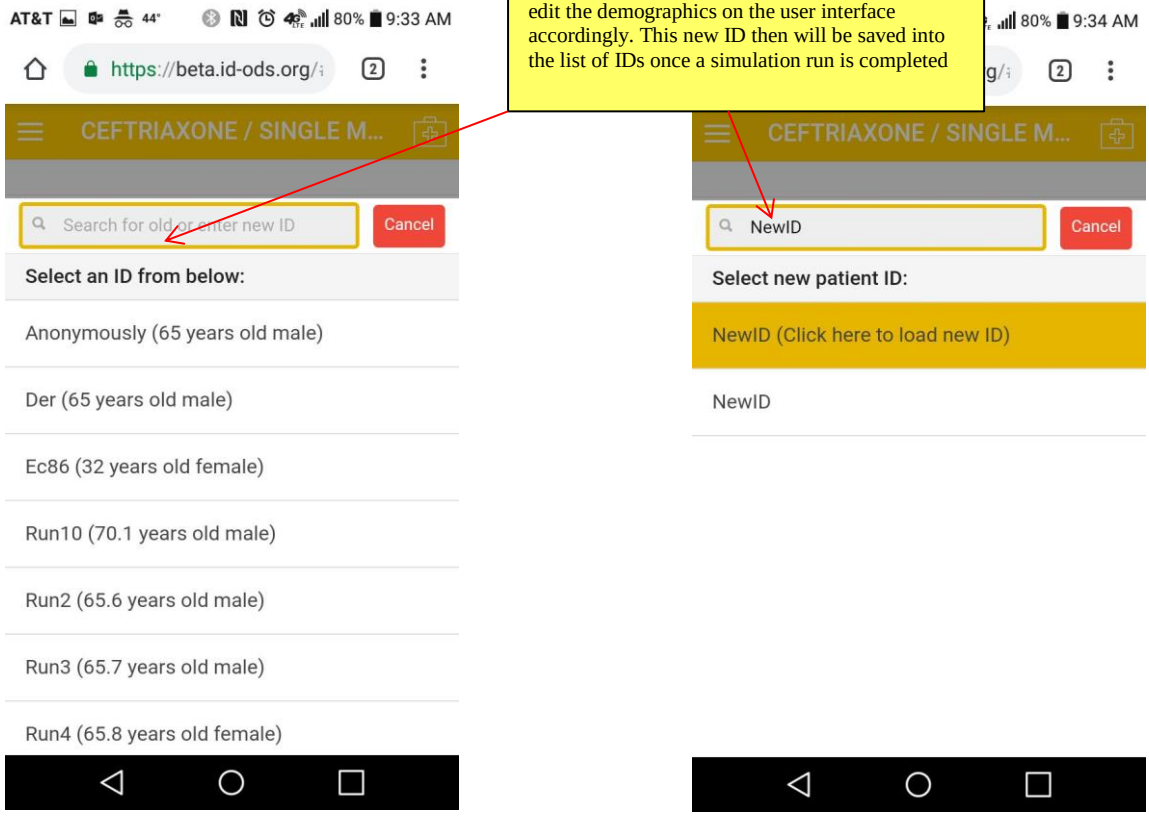


General overview of the Patient record management tab and its general functionality

The tab “Manage Patients” allows the user to conveniently manage profiles of patients that the user previously ran simulations on. After clicking on the tab, a list of profiles with the most recent demographic variables will be displayed to either “Select” or ‘Deleate”. Once selected, the profile will be loaded into the user interface of the drug the simulations are intended for.

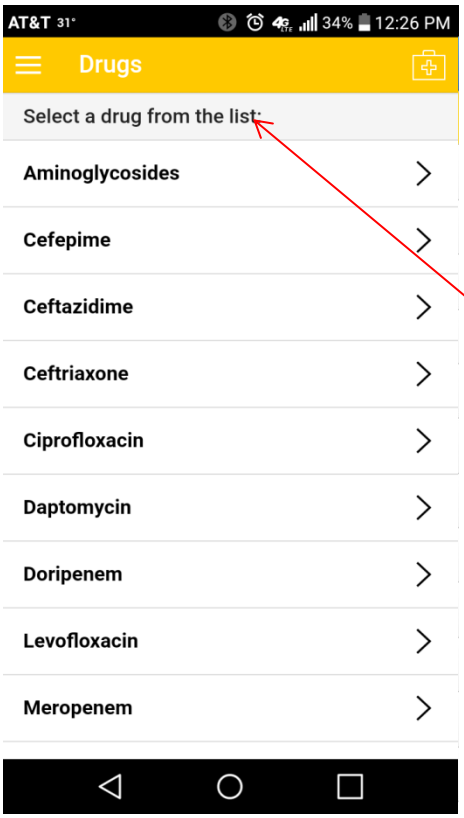


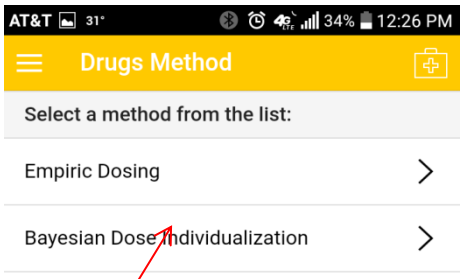
The loading of previously simulated profiles will also be prompted through the Patient ID field of the individual drug interface. Once presented, the user may search for and select an existing profile from the list below or enter a new unique ID and edit the demographics on the user interface accordingly. This new ID then will be saved into the list of IDs once a simulation run is completed



General overview of the a priori dosing and the Bayesian user interface using the Vancomycin and the Aminoglycosides example on an Android device

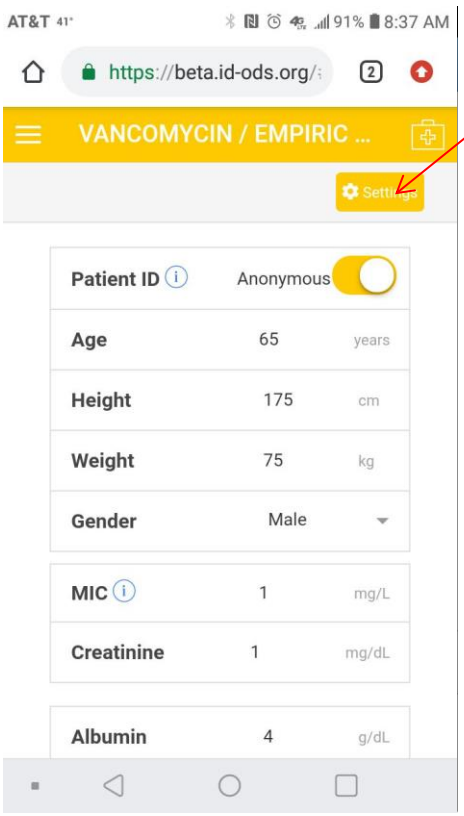
I. User Interface and data input

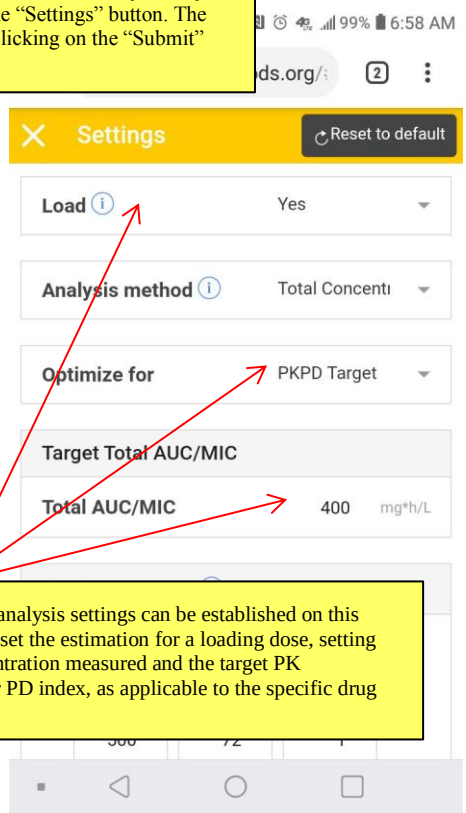




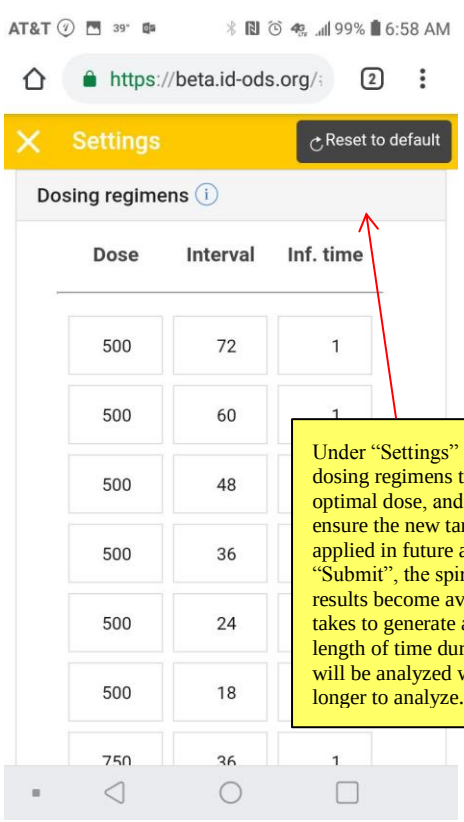
User will select "Vancomycin" from the list of available antibiotics. Once selected, the option of selecting "Empiric Dosing" and "Bayesian Dose Individualization" is displayed.

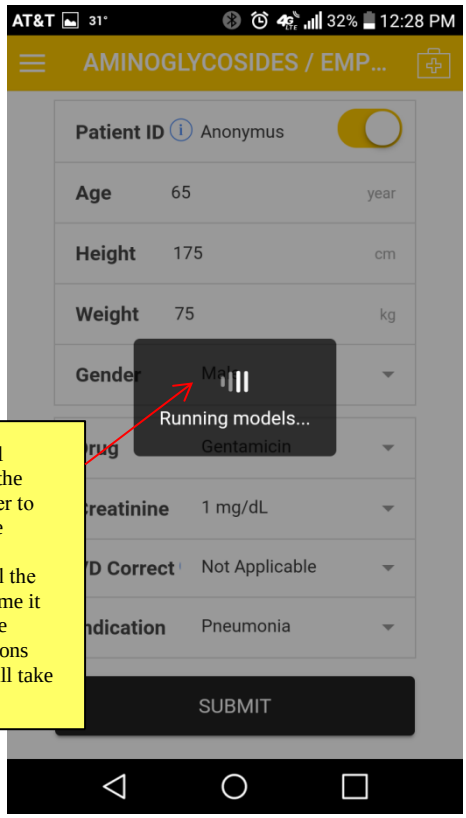
After making the selection, the demographic and laboratory information entry interface will display. User may click/tap on the small "i" icons to gain valuable information about the drug modeling process or data entry requirements. The target concentrations or PKPD index for analysis may be edited by clicking on the "Settings" button. The analysis will begin by clicking on the "Submit" button.



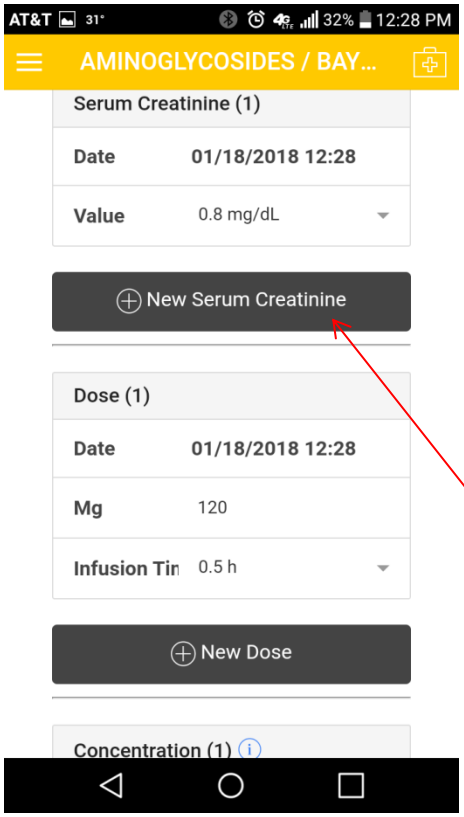


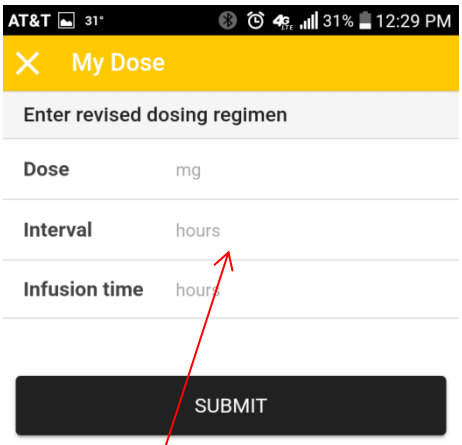
Target PK or PD analysis settings can be established on this page, allowing to set the estimation for a loading dose, setting the type of concentration measured and the target PK concentration/s or PD index, as applicable to the specific drug





Under "Settings" the user may enter several dosing regimens to be used in establishing the optimal dose, and must click "Save" in order to ensure the new targets and regimens will be applied in future analysis. Once clicked on "Submit", the spinning wheel will turn until the results become available for display. The time it takes to generate a report will depend on the length of time during which the concentrations will be analyzed where longer time span will take longer to analyze.



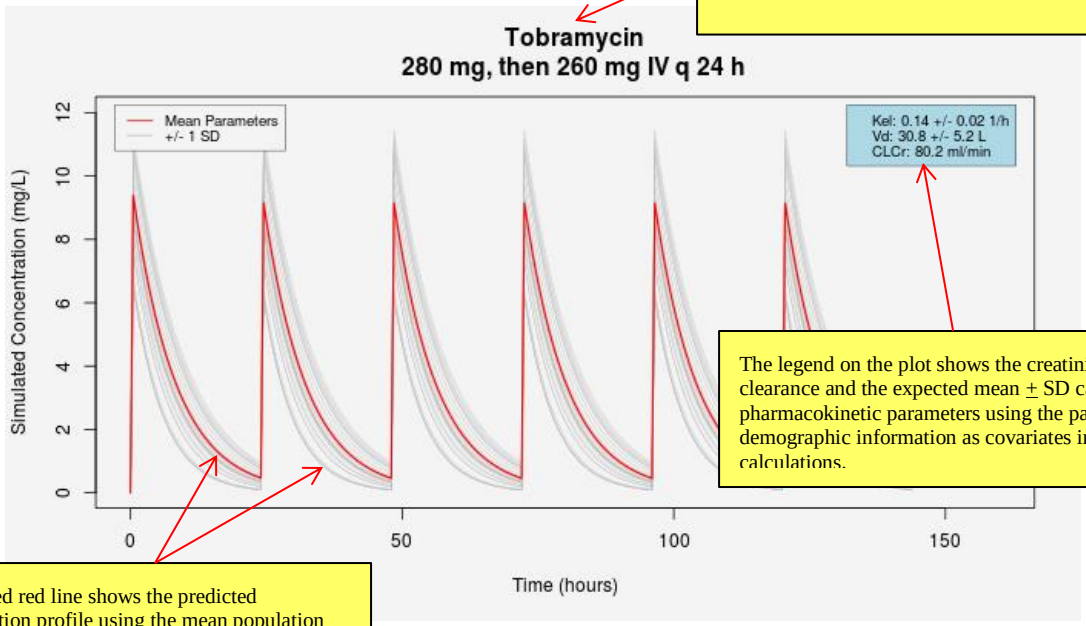


The Bayesian analysis interface provides input fields for relevant laboratory and dosing information. To add an event, the user would click on the "New …" button, while to remove an event would click on the "Remove …" button. If the user wishes to evaluate a regimen different from the one suggested by the application based on the target levels specified, the user may click on the "MyDose" button in the results display window and enter a custom regimen to be analyzed.

II. Output plots

A. A – priory dosing

The plot title displays the calculated drug‘s name, the loading dose, and the subsequent maintenance dose, followed by the dosing interval.

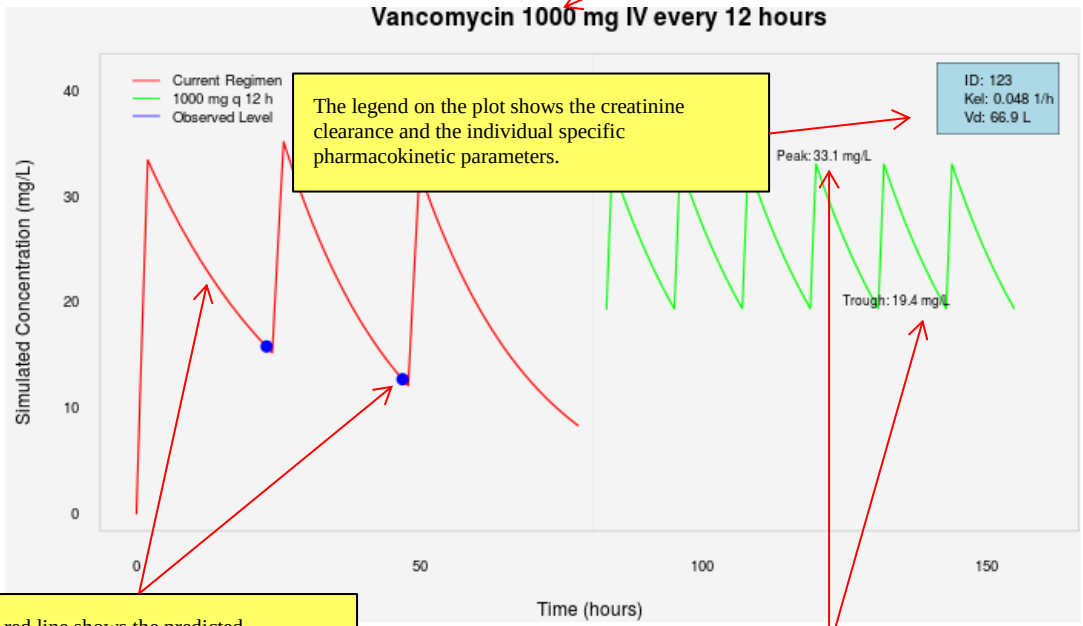


The legend on the plot shows the creatinine clearance and the expected mean ± SD calculated pharmacokinetic parameters using the patient demographic information as covariates in the calculations.

The plotted red line shows the predicted concentration profile using the mean population parameter value, versus the grey lines shows the simulated concentrations using the population parameters in ± SD interval.

B. Inverse Bayesian modeling

The plot title displays the calculated drug‘s name, the optimal dose (rounded), followed by the optimal dosing interval designed to achieve the target concentrations. The calculation is based on the assumption of steady state.

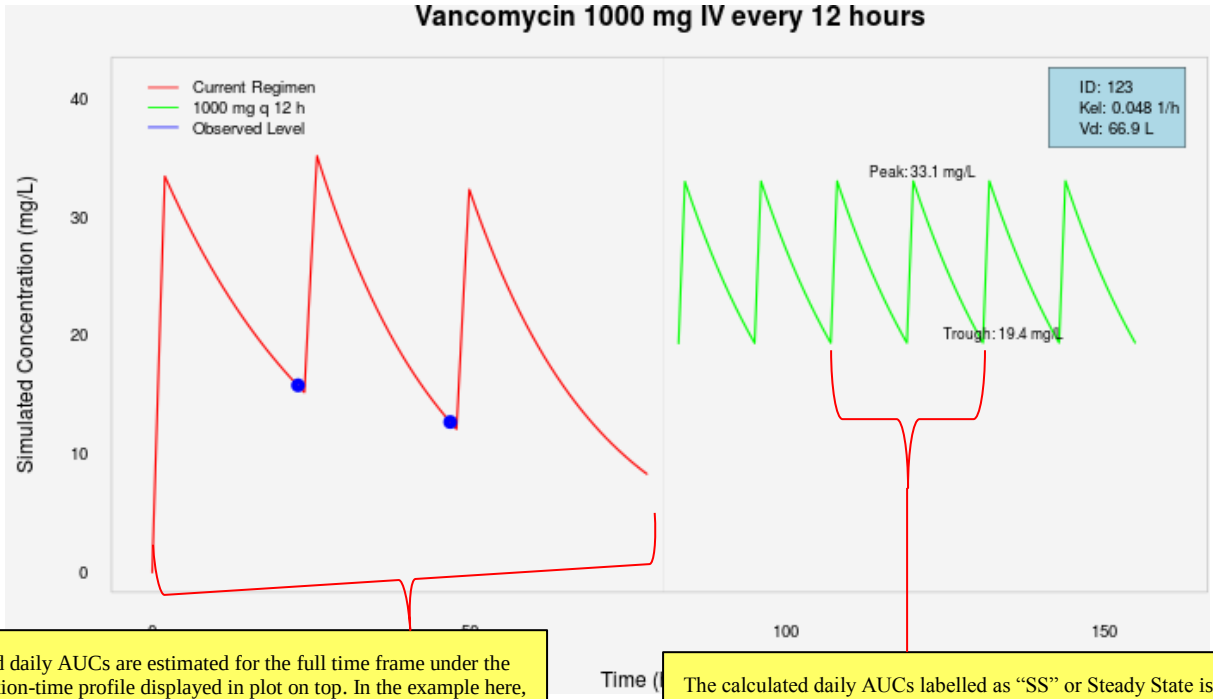


The legend on the plot shows the creatinine clearance and the individual specific pharmacokinetic parameters.

The plotted red line shows the predicted concentration - time profile using the individual pharmacokinetic parameter values established by fitting the measured concentrations (blue dots) with the Bayesian system.

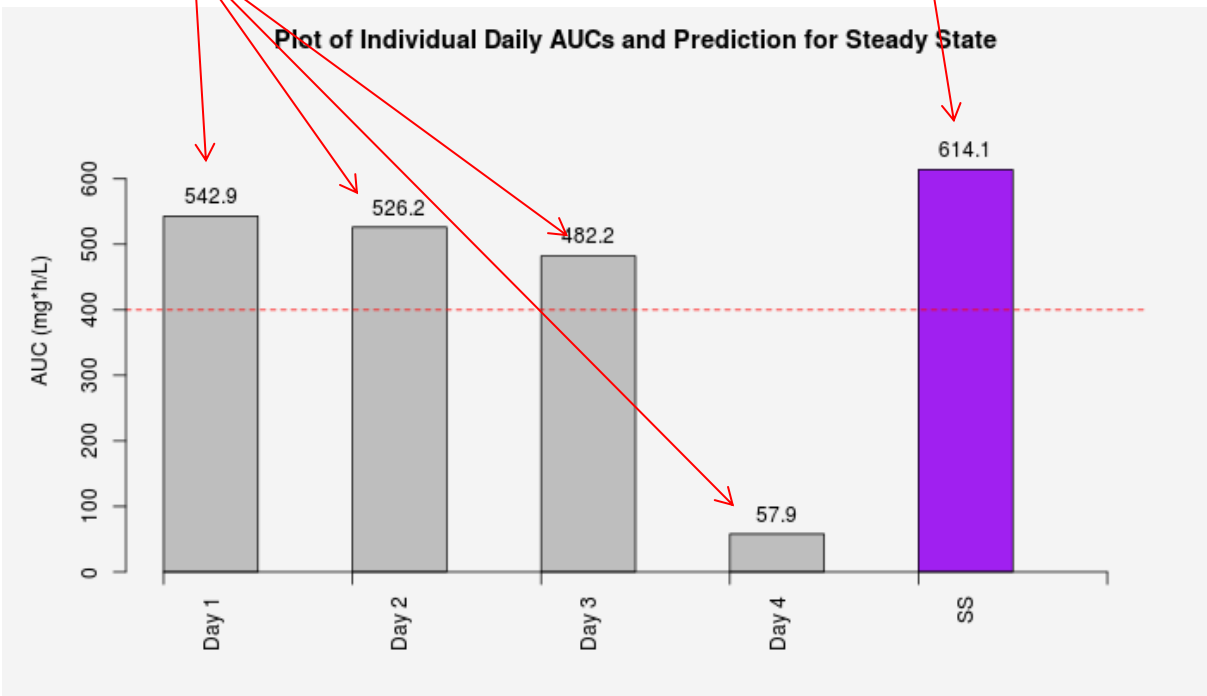
The plot also displays expected peak and trough levels associated with the optimal dosing regimen.

C. Individual drug exposure analysis plots

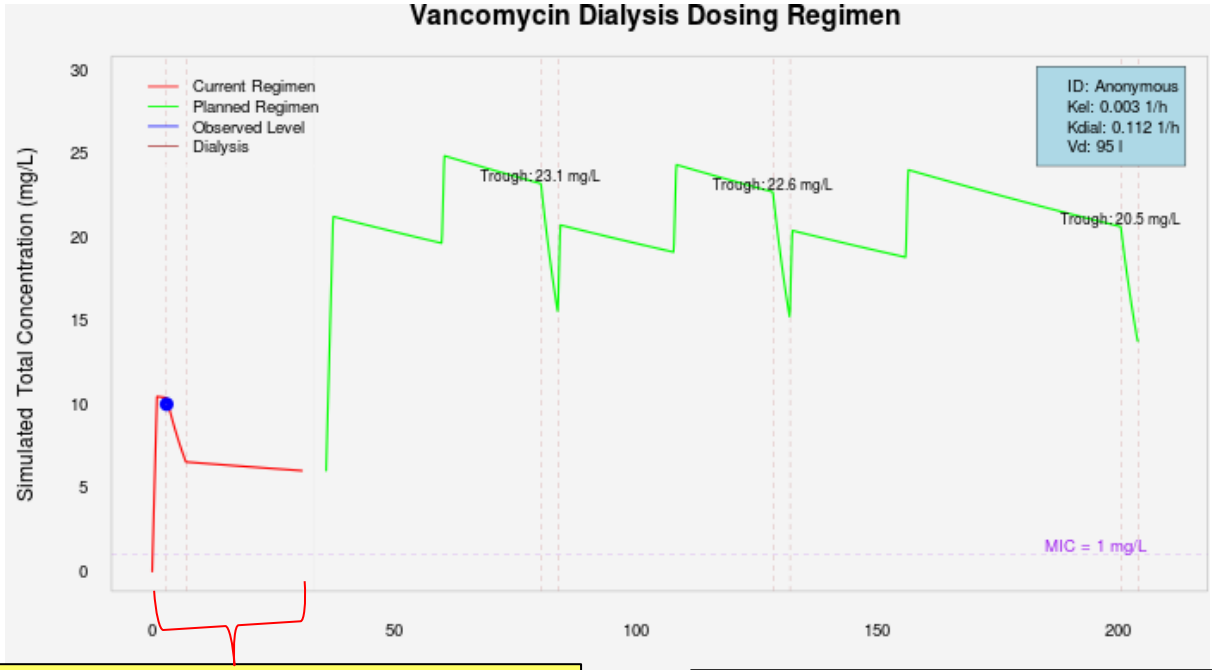


The calculated daily AUCs are estimated for the full time frame under the red concentration-time profile displayed in plot on top. In the example here, we plotted approximately 75 hours' worth of concentration profile; hence the AUCs are calculated for 3 full days, then for 3 hours only on day 4. Thus day 4 represents only a fraction of the full day's AUC. This fractional AUC on the last day/s usually results from a default setting that adds a total of 2 hours to the latest time point used during the Bayesian fitting procedure in addition to the fractional day resulting from data entry, which allows for the observation of drug concentration after the last dose.

The calculated daily AUCs labelled as "SS" or Steady State is estimated for 24 hours of the recommended steady state dose.

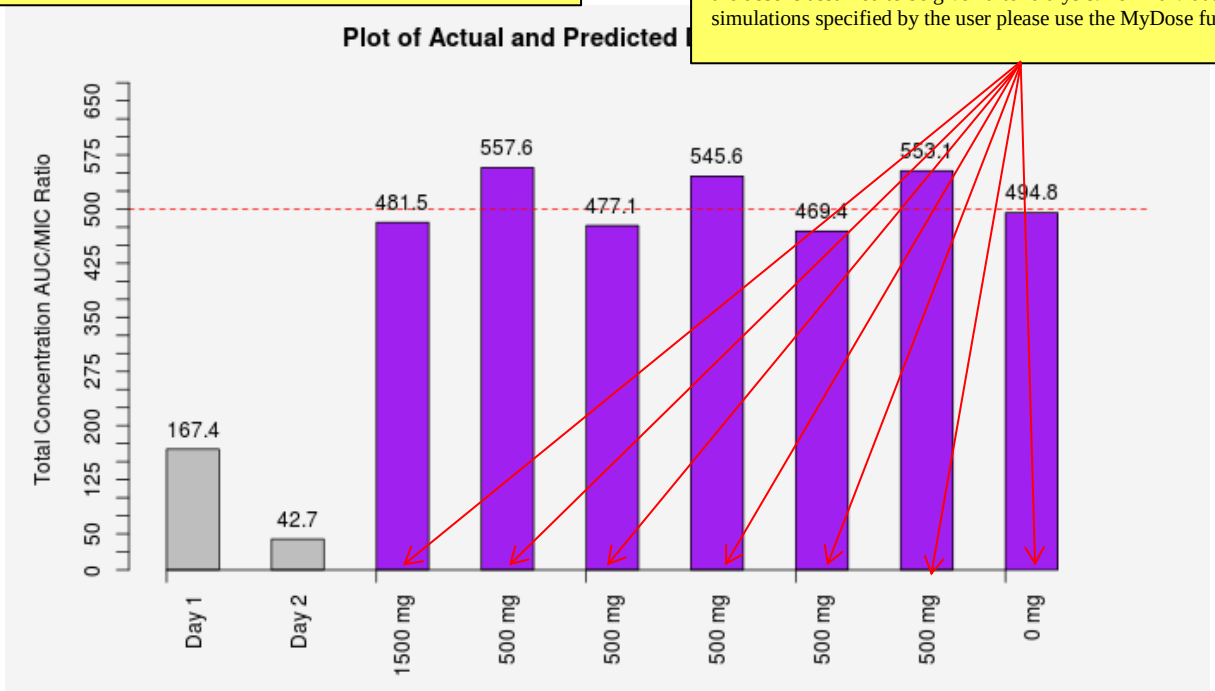


D. Dialysis regimen analysis plots



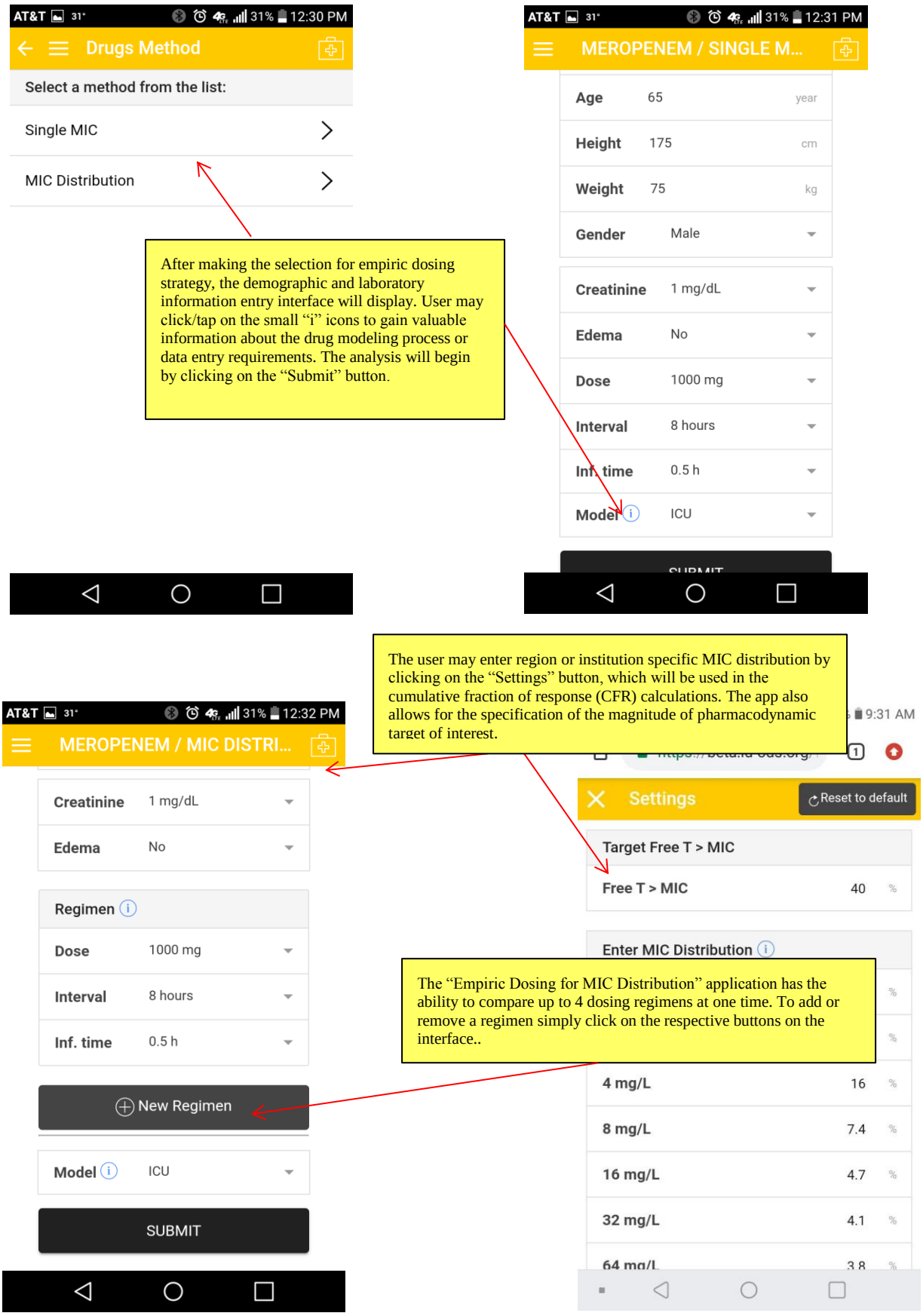
Similar to the individual drug exposure analysis plots, the calculated daily AUCs are estimated for the full time frame under the red concentration-time profile displayed in plot on top. In the example here, we plotted approximately 32 hours' worth of concentration profile; hence the AUCs are calculated for 1 full day, then for 8 hours only on day24. Thus day 2 represents only a fraction of the full day's AUC. This fractional AUC on the last day/s usually results from a default setting that adds a total of 24 hours to the latest time point used during the Bayesian fitting procedure, which allows for the observation of drug concentration after the last dose.

The built in algorithm will calculate the optimal dosing regimen that allows for minimal daily deviation from the target PKPD index specified by the user. A dose will be estimated for 7 days (including a dose of zero mg if that is deemed to be optimal on a given day) assuming 3 dialysis sessions taking place at hour 48, 96 and 168 that lasts for 3 hours. The optimal dose calculated for a given day then will be displayed in the daily AUC plot (purple bars) as the axis labels. According to this example, a dose of 1500 mg should be given on day 1 (immediately), followed by 500 mgs on day 2, 3, 4, 5, and 6, then no dose to be given (0 mg) on day 7. On dialysis days the dose is assumed to be given after dialysis. For individual dose simulations specified by the user please use the MyDose functionality.



General overview of the Monte Carlo Simulation user interface using the Meropenem example on an Android device

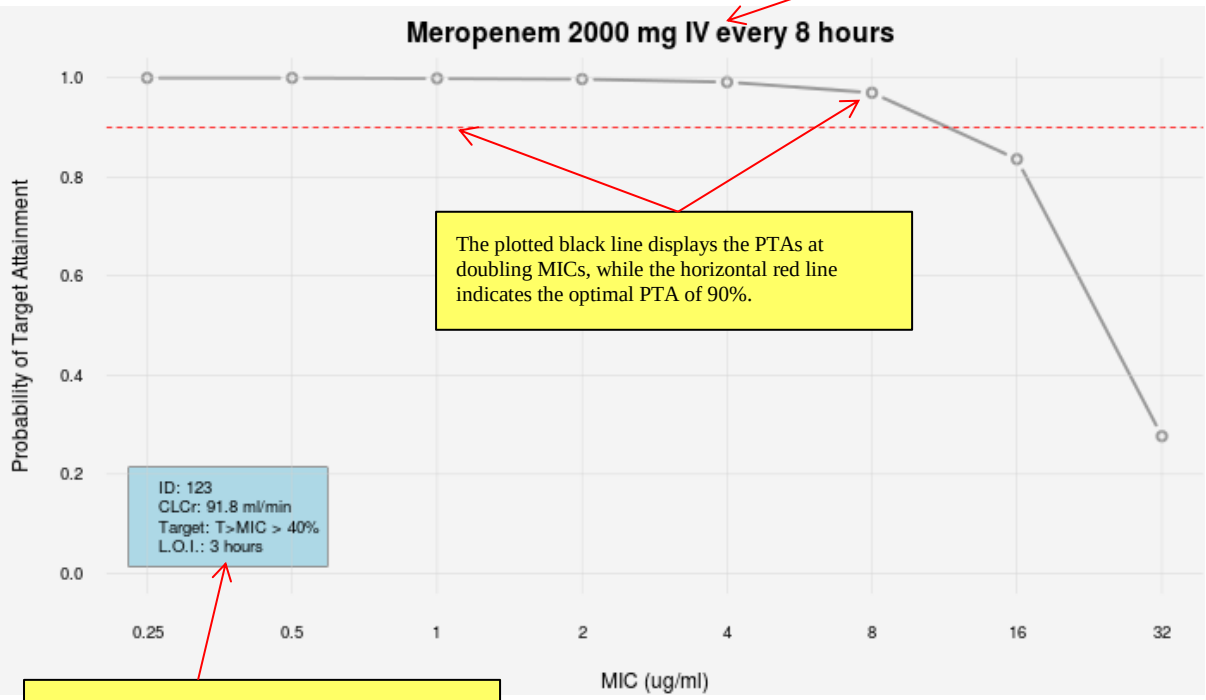
I. User Interface and data input



II. Output plots

The plot title displays the simulated drug's name, the dose, followed by the dosing interval.

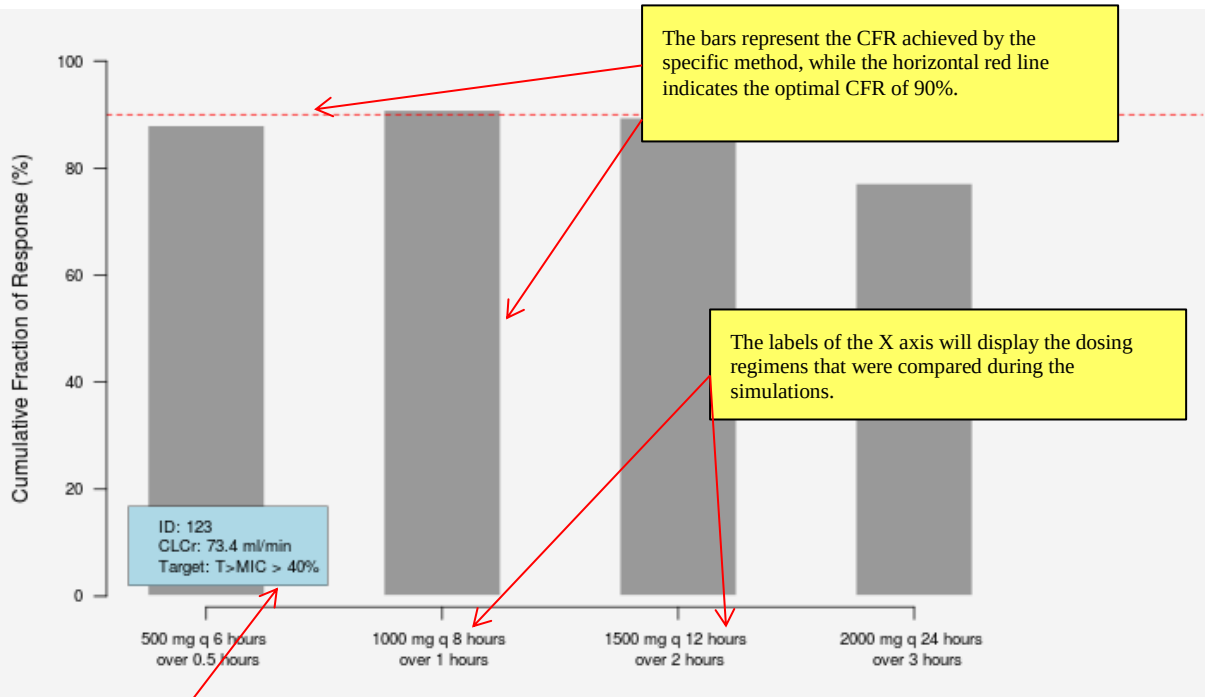
C. Probability of target Attainment (PTA) plots



The plotted black line displays the PTAs at doubling MICs, while the horizontal red line indicates the optimal PTA of 90%.

The legend of the plot contains the ID number, estimated creatinine clearance, the pharmacodynamics target index and the length of infusion (L.O.I.) applied during the simulations

D. Cumulative Fraction of Response (CFR) plots



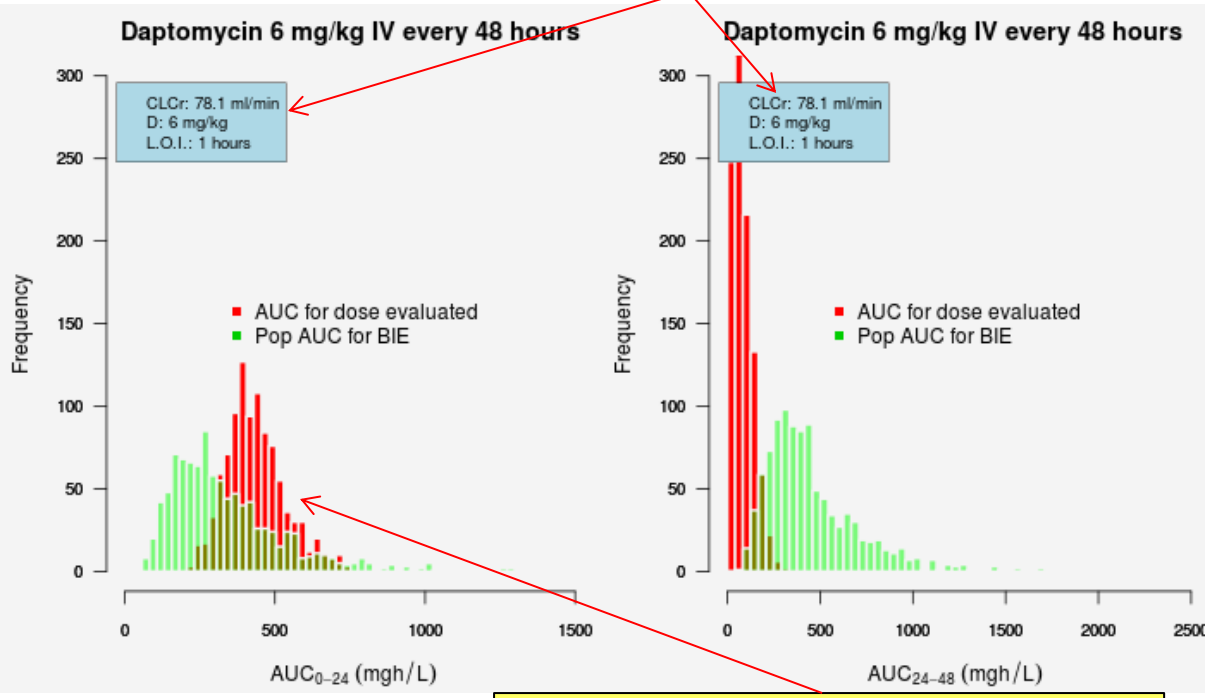
The bars represent the CFR achieved by the specific method, while the horizontal red line indicates the optimal CFR of 90%.

The labels of the X axis will display the dosing regimens that were compared during the simulations.

The legend of the plot contains the ID number, estimated creatinine clearance, and the pharmacodynamics target index applied during the simulations

E. Exposure plots

The legend of the plot contains the estimated creatinine clearance, the dose evaluated, and the length of infusion applied during the simulations



The bi-color histogram shows the distribution of the pharmacokinetic parameter of interest comparatively for the dose evaluated (red) versus the reference distribution (green), where optimal exposure would be represented by a perfect overlap of the histograms. 48h intervals will provide AUCs for the first and second 24 h portions.

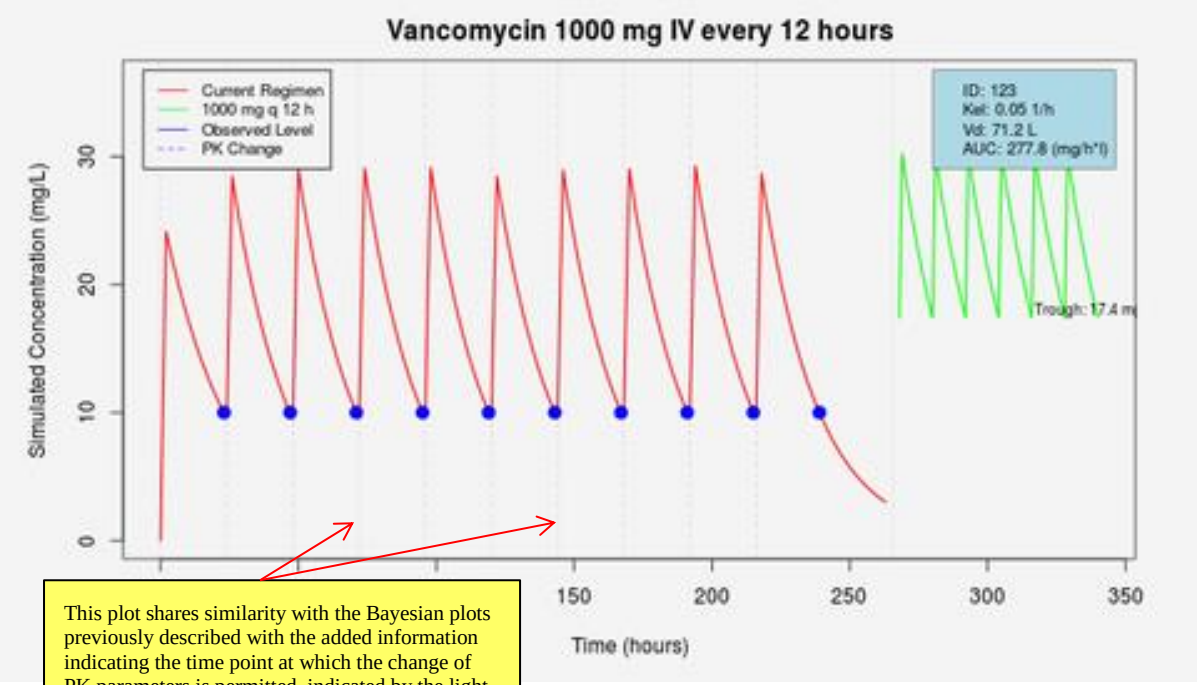
F. Detailed pharmacokinetic and pharmacodynamics analysis report

PATIENT ID	DOB	MR NUMBER	WARD	ROOM	PROVIDER ID
123	01/01/67	123456	MICU	2	MD-1

Age (years)	Height (cm)	Weight (kg)	Sex	ClCr (ml/min)
65	175	85	M	73.4

Detailed PKPD analysis reports show patient demographic and institution specific information suitable for inclusion in the medical record.

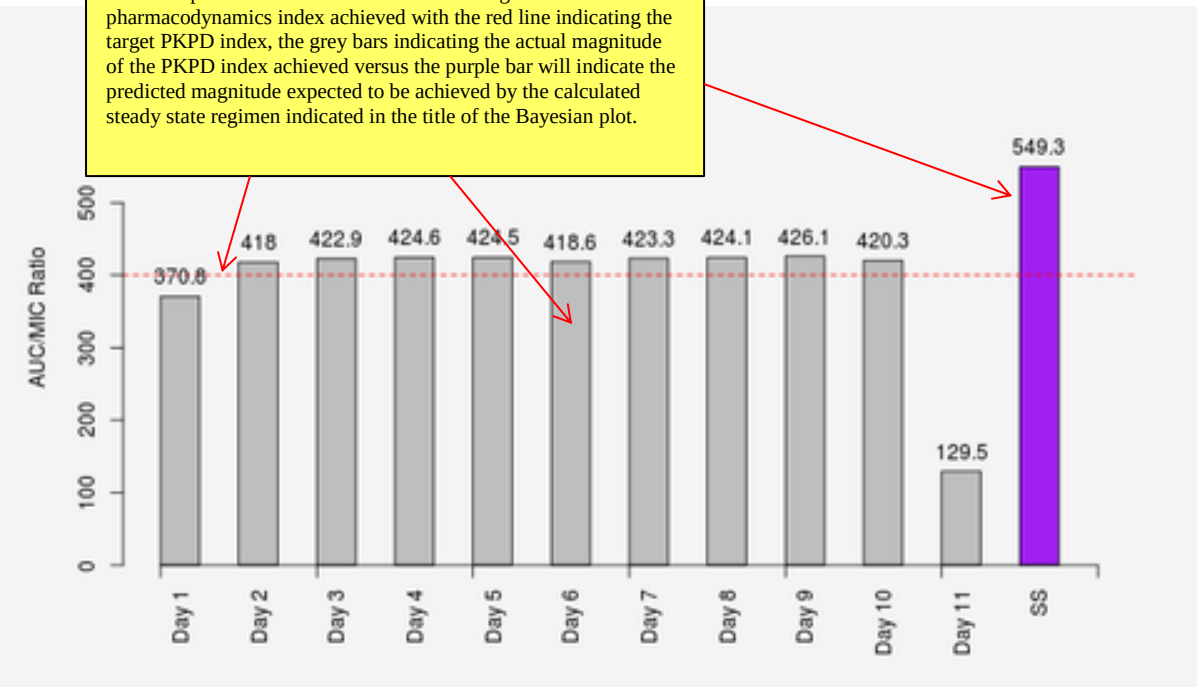
1. Patient Demographics



This plot shares similarity with the Bayesian plots previously described with the added information indicating the time point at which the change of PK parameters is permitted, indicated by the light dotted purple lines.

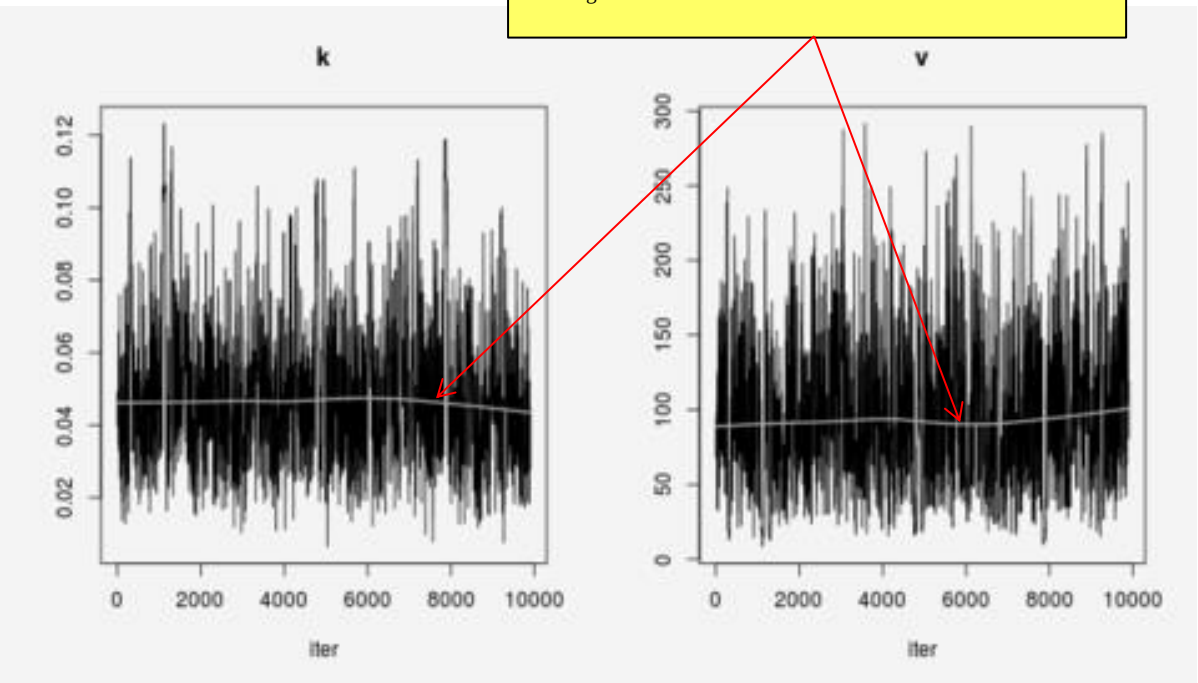
2. Plot of Predicted and Observed Concentrations

The third plot shows the breakdown of the magnitude of the pharmacodynamics index achieved with the red line indicating the target PKPD index, the grey bars indicating the actual magnitude of the PKPD index achieved versus the purple bar will indicate the predicted magnitude expected to be achieved by the calculated steady state regimen indicated in the title of the Bayesian plot.

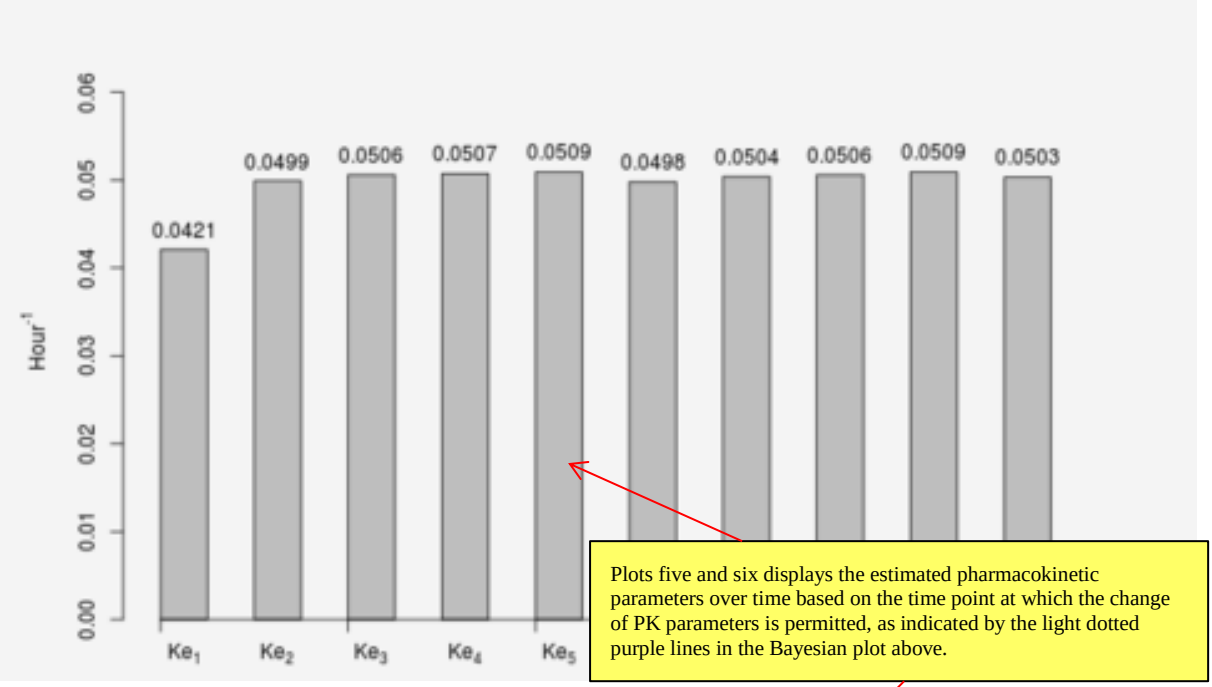


3. Plot of Daily AUC/MIC Ratios

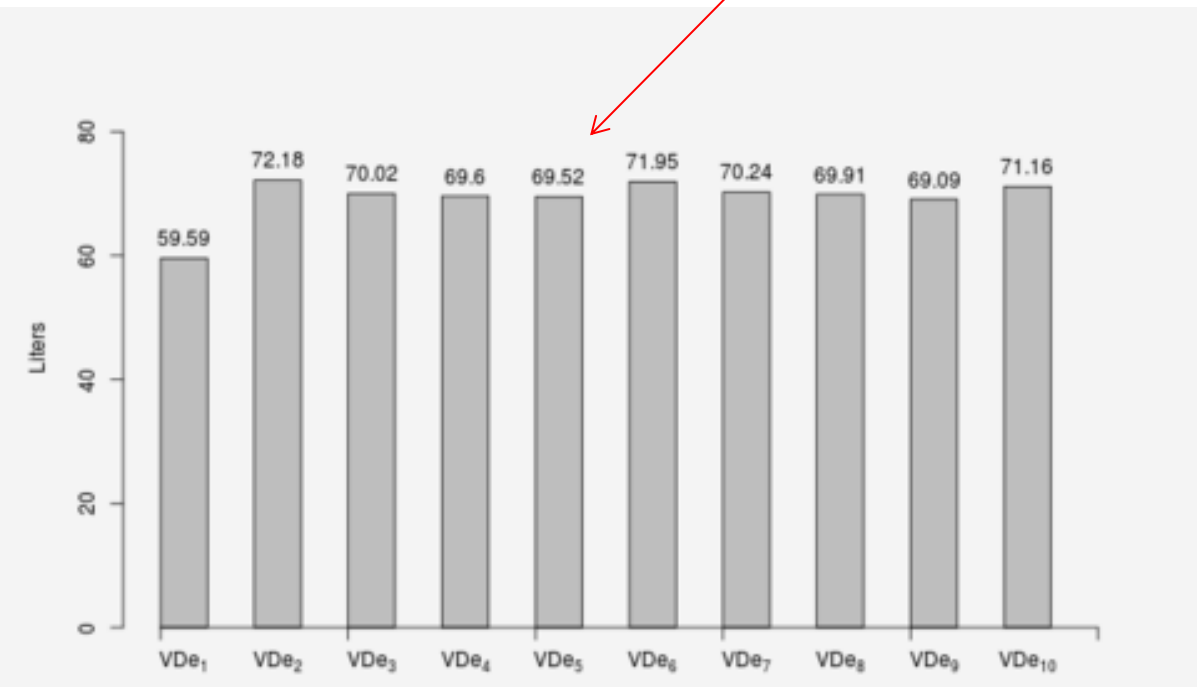
The fourth plot shows the convergence plots of the Markov chains, where a nearly horizontal grey line indicates reasonable convergence has been achieved..



4. Parameter Convergence Plots



5. Plot of Individual Elimination Rate Constants



6. Plot of Individual Volume of Distributions

General Workflow

The ID-ODS™ applications are powered by a cloud-based Application Programming Interface, built on Ruby on Rails and the R statistical programming language and software environment. In practice, the ID-ODS™ applications send the user-initialized modeling requests to the ID-ODS™ servers via encrypted (HTTPS) channel, then the servers evaluate the statistical models and computations, and return the results to the ID-ODS™ applications to render to the user. This centralized workflow provides a high-performant computing environment for the consumers available from any devices, with the advantage of optionally syncing user data between those automatically. A high-level overview on the infrastructure is as follows (see figure below): The user-specified parameters from the ID-ODS™ application [1] are passed to ID-ODS™ website [2], which seamlessly transmits the model parameters to the ID-ODS™ API over a secure channel for evaluation. The channel is backed up by a content delivery network [3] that is also speeding up connection besides making it possible to provide high availability for the ID-ODS™ users. The cluster of webservers [4] processes the queries and reads the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers. The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks can use any of the numerous, currently more than 10,000 user contributed packages found on CRAN, and the templates can call even GRASS for spatial analysis or OpenBUGS [7] as a Bayesian interface. The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Drug models

ID – ODS™ system utilizes peer reviewed, published pharmacokinetic models in the calculation of drug specific kinetic and dynamic indices. The list of antibiotics and respective pharmacokinetic models coded in the application are as follows:

1. *Aminoglycosides*

Pai MP, Nafziger AN, Bertino JS. Simplified Estimation of Aminoglycoside Pharmacokinetics in Underweight and Obese Adult Patients. Antimicrobial Agents and Chemotherapy. 2011;55(9):4006-4011. doi:10.1128/AAC.00174-11.

2. *Amoxicillin and clavulanic acid*

Carlier M, Noë M, De Waele JJ, Stove V, Verstraete AG, Lipman J, Roberts JA. Population pharmacokinetics and dosing simulations of amoxicillin/clavulanic acid in critically ill patients. J Antimicrob Chemother. 2013 Nov;68(11):2600-8

3. *Cefepime*

Nicasio AM, Ariano RE, Zelenitsky SA, et al. Population Pharmacokinetics of High-Dose, Prolonged-Infusion Cefepime in Adult Critically Ill Patients with Ventilator-Associated Pneumonia . Antimicrobial Agents and Chemotherapy. 2009;53(4):1476-1481. doi:10.1128/AAC.01141-08.

Tam VH, McKinnon PS, Akins RL, Drusano GL, Rybak MJ. Pharmacokinetics and Pharmacodynamics of Cefepime in Patients with Various Degrees of Renal Function. Antimicrobial Agents and Chemotherapy. 2003;47(6):1853-1861. doi:10.1128/AAC.47.6.1853-1861.2003.

4. *Ceftazidime*

Georges B, Conil J-M, Seguin T, et al. Population Pharmacokinetics of Ceftazidime in Intensive Care Unit Patients: Influence of Glomerular Filtration Rate, Mechanical Ventilation, and Reason for Admission . Antimicrobial Agents and Chemotherapy. 2009;53(10):4483-4489. doi:10.1128/AAC.00430-09.

5. *Ceftriaxone*

Garot D, Respaud R, Lanotte P, et al. Population pharmacokinetics of ceftriaxone in critically ill septic patients: a reappraisal. British Journal of Clinical Pharmacology. 2011;72(5):758-767. doi:10.1111/j.1365-2125.2011.04005.x.

6. Ciprofloxacin

Khachman, D., Conil, J., Georges, B., Saivin, S., Houin, G., Toutain, P., & Laffont, C. M. (2011). Optimizing ciprofloxacin dosing in intensive care unit patients through the use of population pharmacokinetic-pharmacodynamic analysis and Monte Carlo simulations. Journal of Antimicrobial Chemotherapy, 66(8), 1798-1809. doi:10.1093/jac/dkr220

7. Daptomycin

Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population Pharmacokinetics of Daptomycin. Antimicrobial Agents and Chemotherapy. 2004;48(8):2799-2807. doi:10.1128/AAC.48.8.2799-2807.2004.

8. Doripenem

Abdul-Aziz MH, Abd Rahman AN, Mat-Nor M-B, et al. Population Pharmacokinetics of Doripenem in Critically Ill Patients with Sepsis in a Malaysian Intensive Care Unit. Antimicrobial Agents and Chemotherapy. 2016;60(1):206-214. doi:10.1128/AAC.01543-15.

9. Flucloxacillin

Xie et al, unpublished at this time.

10. Levofloxacin

Preston SL, Drusano GL, Berman AL, et al. Levofloxacin Population Pharmacokinetics and Creation of a Demographic Model for Prediction of Individual Drug Clearance in Patients with Serious Community-Acquired Infection. Antimicrobial Agents and Chemotherapy. 1998;42(5):1098-1104.

11. Meropenem

Crandon, J. L., Ariano, R. E., Zelenitsky, S. A., Nicasio, A. M., Kuti, J. L., & Nicolau, D. P. (2010). Optimization of meropenem dosage in the critically ill population based on renal function. Intensive Care Medicine, 37(4), 632-638. doi:10.1007/s00134-010-2105-0

Li, C., Kuti, J. L., Nightingale, C. H., & Nicolau, D. P. (2006). Population Pharmacokinetic Analysis and Dosing Regimen Optimization of Meropenem in Adult Patients. The Journal of Clinical Pharmacology, 46(10), 1171-1178. doi:10.1177/0091270006291035

Doh, K., Woo, H., Hur, J., Yim, H., Kim, J., Chae, H., . . . Yim, D. (2010). Population pharmacokinetics of meropenem in burn patients. Journal of Antimicrobial Chemotherapy, 65(11), 2428-2435. doi:10.1093/jac/dkq317

12. Piperacillin and tazobactam

Felton TW, Roberts JA, Lodise TP, et al. Individualization of Piperacillin Dosing for Critically Ill Patients: Dosing Software To Optimize Antimicrobial Therapy. Antimicrobial Agents and Chemotherapy. 2014;58(7):4094-4102. doi:10.1128/AAC.02664-14.

Patel N, Scheetz MH, Drusano GL, Lodise TP. Identification of Optimal Renal Dosage Adjustments for Traditional and Extended-Infusion Piperacillin-Tazobactam Dosing Regimens in Hospitalized Patients . Antimicrobial Agents and Chemotherapy. 2010;54(1):460-465. doi:10.1128/AAC.00296-09.

13. Polymixin

Sandri, A. M., Landersdorfer, C. B., Jacob, J., Boniatti, M. M., Dalarosa, M. G., Falci, D. R., Zavascki, A. P. (2013). Population Pharmacokinetics of Intravenous Polymyxin B in Critically Ill Patients: Implications for Selection of Dosage Regimens. Clinical Infectious Diseases, 57(4), 524-531. doi:10.1093/cid/cit334

14. Telavancin

Samara E, Shaw J-P, Barriere SL, Wong SL, Worboys P. Population Pharmacokinetics of Telavancin in Healthy Subjects and Patients with Infections. Antimicrobial Agents and Chemotherapy. 2012;56(4):2067-2073. doi:10.1128/AAC.05915-11.

15. Tigecycline

Van Wart SA, Owen JS, Ludwig EA, Meagher AK, Korth-Bradley JM, Cirincione BB. Population Pharmacokinetics of Tigecycline in Patients with Complicated Intra-Abdominal or Skin and Skin Structure Infections . Antimicrobial Agents and Chemotherapy. 2006;50(11):3701-3707. doi:10.1128/AAC.01636-05.

Rubino CM, Forrest A, Bhavnani SM, et al. Tigecycline Population Pharmacokinetics in Patients with Community- or Hospital-Acquired Pneumonia . Antimicrobial Agents and Chemotherapy. 2010;54(12):5180-5186. doi:10.1128/AAC.01414-09.

16. Vancomycin

Neely MN1, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, Lodise TP. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother. 2014;58(1):309-16

Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. Antimicrobial Agents and Chemotherapy. 1984;25(4):433-437.

Ariano RE1, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. Am J Kidney Dis. 2005 Oct;46(4):681-7.

Peer reviewed manuscripts including ID-ODS™

M. L. Avent, B. A. Rogers. Optimising antimicrobial therapy through the use of Bayesian dosing programs. International Journal of Clinical Pharmacy, Published on-line 8-7-2019.

Dhaese SA, Farkas A, Colin P, Lipman J, Stove V, Verstraete AG, Roberts JA, De Waele JJ. Population pharmacokinetics and evaluation of the predictive performance of pharmacokinetic models in critically ill patients receiving continuous infusion meropenem: a comparison of eight pharmacokinetic models. J Antimicrob Chemother. 2018 Oct 30.

Emily L. Heil, David P. Nicolau, Andras Farkas, PharmD, Jason A. Roberts, and Kerri A. Thom.Pharmacodynamic target attainment for cefepime, meropenem and piperacillin/tazobactam using a pharmacokinetic/pharmacodynamic-based dosing calculator in critically ill patients. Antimicrobial Agents and Chemotherapy, published online ahead of print on September 6, 2016

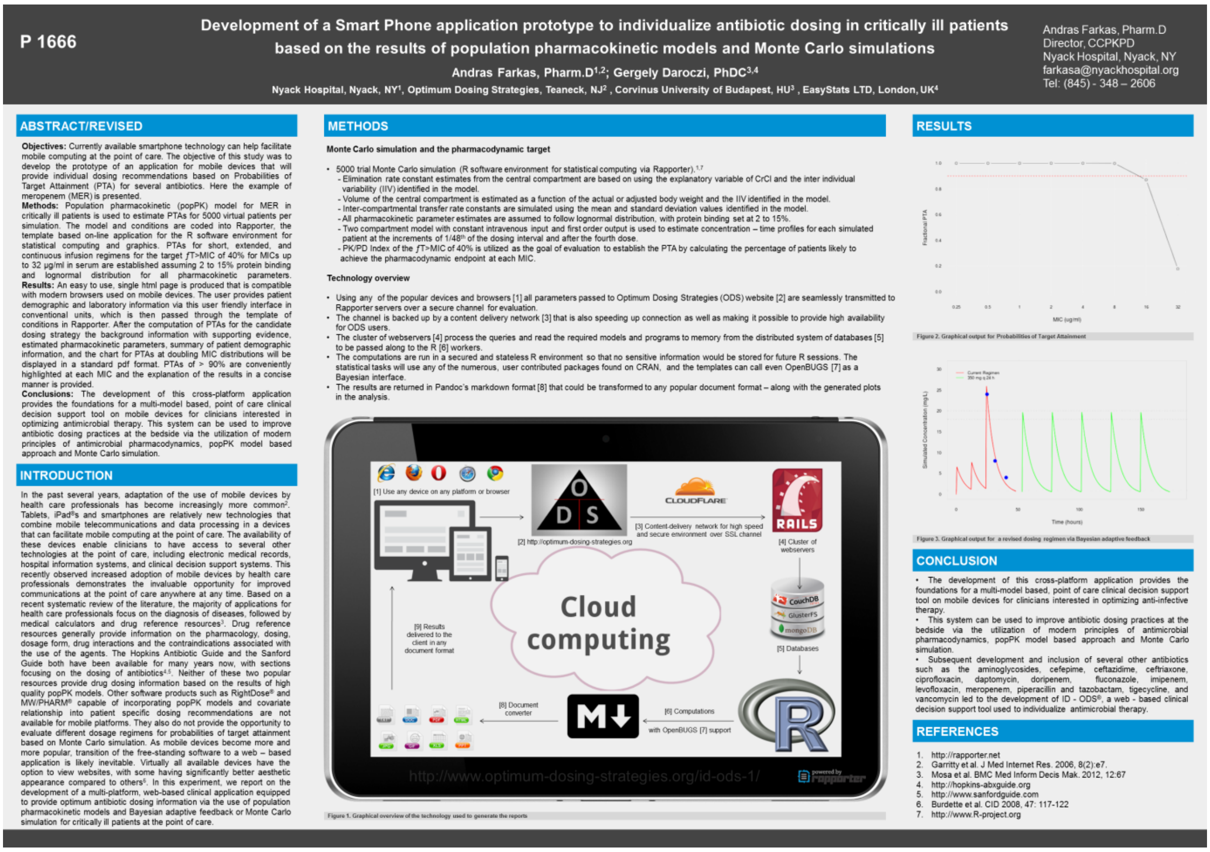
Andras Farkas, Gergely Daroczi, Philip Villasurda, Michael Dolton, Midori Nakagaki, Jason A Roberts; Comparative evaluation of the predictive performance of three different structural population pharmacokinetic models to predict future voriconazole concentrations. Antimicrobial Agents and Chemotherapy, published online ahead of print on September 6, 2016

Delgado-Valverde M, Torres E, Valiente-Mendez A, Almirante B, Gómez-Zorrilla S, Borrell N, Corzo JE, Gurgui M, Almela M, García-Álvarez L, Fontecoba-Sánchez MC, Martínez-Martínez L, Cantón R, Praena J, Causse M, Gutiérrez-Gutiérrez B, Roberts JA, Farkas A, Pascual Á, Rodríguez-Baño J; REIPI/GEIH-SEIMC BACTERAEMIA-MIC group; Impact of the MIC of piperacillin/tazobactam on the outcome for patients with bacteraemia due to Enterobacteriaceae: the Bacteraemia-MIC project. 2016, Journal of Antimicrobial Chemotherapy, 71(2):521-30

Gloria Wong, Andras Farkas, Rachel Sussman, Gergely Daroczi, William W Hope, Jeffrey Lipman, Jason A Roberts; Comparison of the accuracy and precision of pharmacokinetic equations to predict free meropenem concentrations in critically ill patients. Antimicrobial Agents and Chemotherapy, published online ahead of print on 15 December 2014

Jason A Roberts, Mohd H Abdul-Aziz, Jeffrey Lipman, et al., on behalf of The International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases; Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. 2014, The Lancet Infectious Diseases, 14 (6): 441 – 53

Peer reviewed conference papers including ID-ODS™



P 1666

Development of a Smart Phone application prototype to individualize antibiotic dosing in critically ill patients based on the results of population pharmacokinetic models and Monte Carlo simulations

Andras Farkas, Pharm.D[1,2]; Gergely Daroczi, PhDC[3,4]

Nyack Hospital, Nyack, NY[1], Optimum Dosing Strategies, Teaneck, NJ[2], Corvinus University of Budapest, HU[3], EasyStats LTD, London, UK[4]

Andras Farkas, Pharm.D
Director, CCPKPD
Nyack Hospital, Nyack, NY
farkasa@nyackhospital.org
Tel: (845) - 348 – 2606

ABSTRACT/REVISED

Objectives: Currently available smartphone technology can help facilitate mobile computing at the point of care. The objective of this study was to develop the prototype of an application for mobile devices that will provide individual dosing recommendations based on Probabilities of Target Attainment (PTA) for several antibiotics. Here the example of meropenem (MER) is presented.
Methods: Population pharmacokinetic (popPK) model for MER in critically ill patients is used to estimate PTAs for 5000 virtual patients per simulation. The model and conditions are coded into Rapporter, the template based on-line application for the R software environment for statistical computing and graphics. PTAs for short, extended, and continuous infusion regimens for the target ƒT>MIC of 40% for MICs up to 32 µg/ml in serum are established assuming 2 to 15% protein binding and lognormal distribution for all pharmacokinetic parameters.
Results: An easy to use, single html page is produced that is compatible with modern browsers used on mobile devices. The user provides patient demographic and laboratory information via this user friendly interface in conventional units, which is then passed through the template of conditions in Rapporter. After the computation of PTAs for the candidate dosing strategy the background information with supporting evidence, estimated pharmacokinetic parameters, summary of patient demographic information, and the chart for PTAs at doubling MIC distributions will be displayed in a standard pdf format. PTAs of > 90% are conveniently highlighted at each MIC and the explanation of the results in a concise manner is provided.
Conclusions: The development of this cross-platform application provides the foundations for a multi-model based, point of care clinical decision support tool on mobile devices for clinicians interested in optimizing antimicrobial therapy. This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation.

INTRODUCTION

In the past several years, adaptation of the use of mobile devices by health care professionals has become increasingly more common[2]. Tablets, iPad®s and smartphones are relatively new technologies that combine mobile telecommunications and data processing in a devices that can facilitate mobile computing at the point of care. The availability of these devices enable clinicians to have access to several other technologies at the point of care, including electronic medical records, hospital information systems, and clinical decision support systems. This recently observed increased adoption of mobile devices by health care professionals demonstrates the invaluable opportunity for improved communications at the point of care anywhere at any time. Based on a recent systematic review of the literature, the majority of applications for health care professionals focus on the diagnosis of diseases, followed by medical calculators and drug reference resources[3]. Drug reference resources generally provide information on the pharmacology, dosing, dosage form, drug interactions and the contraindications associated with the use of the agents. The Hopkins Antibiotic Guide and the Sanford Guide both have been available for many years now, with sections focusing on the dosing of antibiotics[4,5]. Neither of these two popular resources provide drug dosing information based on the results of high quality popPK models. Other software products such as RightDose® and MW/PHARM® capable of incorporating popPK models and covariate relationship into patient specific dosing recommendations are not available for mobile platforms. They also do not provide the opportunity to evaluate different dosage regimens for probabilities of target attainment based on Monte Carlo simulation. As mobile devices become more and more popular, transition of the free-standing software to a web – based application is likely inevitable. Virtually all available devices have the option to view websites, with some having significantly better aesthetic appearance compared to others[6]. In this experiment, we report on the development of a multi-platform, web-based clinical application equipped to provide optimum antibiotic dosing information via the use of population pharmacokinetic models and Bayesian adaptive feedback or Monte Carlo simulation for critically ill patients at the point of care.

METHODS

Monte Carlo simulation and the pharmacodynamic target

- 5000 trial Monte Carlo simulation (R software environment for statistical computing via Rapporter).[1,7]
  - Elimination rate constant estimates from the central compartment are based on using the explanatory variable of CrCl and the inter individual variability (IIV) identified in the model.
  - Volume of the central compartment is estimated as a function of the actual or adjusted body weight and the IIV identified in the model.
  - Inter-compartmental transfer rate constants are simulated using the mean and standard deviation values identified in the model.
  - All pharmacokinetic parameter estimates are assumed to follow lognormal distribution, with protein binding set at 2 to 15%.
  - Two compartment model with constant intravenous input and first order output is used to estimate concentration – time profiles for each simulated patient at the increments of 1/48th of the dosing interval and after the fourth dose.
  - PK/PD Index of the ƒT>MIC of 40% is utilized as the goal of evaluation to establish the PTA by calculating the percentage of patients likely to achieve the pharmacodynamic endpoint at each MIC.

Technology overview

- Using any of the popular devices and browsers [1] all parameters passed to Optimum Dosing Strategies (ODS) website [2] are seamlessly transmitted to Rapporter servers over a secure channel for evaluation.
- The channel is backed up by a content delivery network [3] that is also speeding up connection as well as making it possible to provide high availability for ODS users.
- The cluster of webservers [4] process the queries and read the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers.
- The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks will use any of the numerous, user contributed packages found on CRAN, and the templates can call even OpenBUGS [7] as a Bayesian interface.
- The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Figure 1. Graphical overview of the technology used to generate the reports

RESULTS

Figure 2. Graphical output for Probabilities of Target Attainment

Figure 3. Graphical output for a revised dosing regimen via Bayesian adaptive feedback

CONCLUSION

- The development of this cross-platform application provides the foundations for a multi-model based, point of care clinical decision support tool on mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation.
- Subsequent development and inclusion of several other antibiotics such as the aminoglycosides, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, daptomycin, doripenem, fluconazole, imipenem, levofloxacin, meropenem, piperacillin and tazobactam, tigecycline, and vancomycin led to the development of ID - ODS®, a web - based clinical decision support tool used to individualize antimicrobial therapy.

REFERENCES

1. http://rapporter.net
2. Garritty et al. J Med Internet Res. 2006, 8(2):e7.
3. Mosa et al. BMC Med Inform Decis Mak. 2012, 12:67
4. http://hopkins-abxguide.org
5. http://www.sanfordguide.com
6. Burdette et al. CID 2008, 47: 117-122
7. http://www.R-project.org

EP539

Usage statistics of Individually Designed Optimum Dosing Strategies, a multi-model based online application to individualize antibiotic dosing in critically ill patients

Andras Farkas, Pharm.D[1]; Gergely Daroczi, PhDC[2] ; Jason Roberts, PhD[3,4]

Optimum Dosing Strategies, Bloomingdale, NJ[1] ; Easy Stats LTD, London, UK[2]; Royal Brisbane and Women's Hospital, Brisbane, Australia[3]; Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia[4]

ABSTRACT/REVISED

Objectives: In order to help overcome some of the current challenges for the wide-spread implementation of model based goal oriented dosing of antibiotics, we have launched Individually Designed Optimum Dosing Strategies (ID-ODS™) on the web in late 2012. The objective of this study was to evaluate the utilization of this on-line dosing tool used to facilitate the optimal dosing of sixteen antibiotics via estimation of patient specific Probabilities of Target Attainment (PTA) and Bayesian adaptive feedback.
Methods: Continuous data collection on individual queries was supported by Rapporter®, a data analysis and reporting application for the use of the R® statistical software environment in the cloud. The number of queries on specific antibiotic templates by geolocalized IP address and anonymised parameters were evaluated for CPU time and for the frequency of successfully generated reports.
Results: The website applications were successfully queried 5678 times during the time of evaluation. 85.9 % of all users connected from North America. The remaining 14.1 % of users joined the site mainly from Europe (47.7%), Asia - Pacific region (25.9%), South America (24.2%) and the rest of the world (2.2%). PTAs for Piperacillin and Tazobactam and estimations of empiric dosing regimens for Vancomycin were the most common reasons for utilization, followed by Bayesian analysis of individual Vancomycin and Aminoglycoside concentration information. They accounted for a combined 54.5% of all data management. Cefepime and Meropenem were the second and third most commonly accessed templates for PTA dose optimization, representing 39.1 % of the entire beta - lactam queries together. CPU times differed substantially for templates running PTAs versus the Bayesian models with a mean + SD of 6.88 + 2.08 seconds and 19.16 + 17.12 seconds, respectively. Generating the reports was aborted early 13.5 % of the time, where the reasons for failure were most commonly linked to inaccurate data entry.
Conclusions: The world-wide web availability of this cross-platform application provides the framework for a point of care clinical decision support tool on mobile and stationery devices for practitioners interested in optimizing antimicrobial therapy. During the first year in live environment, the system was ran successfully over five thousand occasions, providing computational results of high complexity under the average of 20 seconds of time. The utilization information collected during this period will also help us further improve the system to minimize rates of template failure due to inaccurate data entry.

INTRODUCTION

In the past several years, adaptation of the use of on-line applications on mobile devices by health care professionals has become increasingly more common. Tablets, iPad®s and smartphones are relatively new technologies that combine mobile telecommunications and data processing in a devices that can facilitate mobile computing at the point of care. This recently observed increased adoption of mobile devices by health care professionals demonstrates the invaluable opportunity for improved communications at the point of care anywhere at any time[1,2]. Drug reference resources generally provide information on the pharmacology, dosing, dosage form, drug interactions and the contraindications associated with the use of the agents. The Hopkins Antibiotic Guide and the Sanford Guide both have been available for many years now, with sections focusing on the dosing of antibiotics[3,4]. Neither of these two popular resources directly provide drug dosing information based on the results of high quality popPK models. They also do not provide the opportunity to evaluate different dosage regimens for probabilities of target attainment based on Monte Carlo simulation. As on-line computing and the use of mobile devices become more and more popular, transition of the free-standing software to a web – based application is likely inevitable. Virtually all available devices have the option to view websites, with some having significantly better aesthetic appearance compared to others[5]. In this experiment, we report on the usage statistics of a multi-platform, web-based clinical application equipped to provide optimum antibiotic dosing information via the use of population pharmacokinetic models and Bayesian adaptive feedback or Monte Carlo simulation for critically ill patients at the point of care.

METHODS

ID – ODS™ Technology Overview [6,7,8]

- Using any of the popular devices and browsers [1] all parameters passed to Optimum Dosing Strategies (ODS) website [2] are seamlessly transmitted to Rapporter servers over a secure channel for evaluation.
- The channel is backed up by a content delivery network [3] that is also speeding up connection as well as making it possible to provide high availability for ODS users.
- The cluster of webservers [4] process the queries and read the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers.
- The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks will use any of the numerous, user contributed packages found on CRAN like the FME package as a Bayesian interface.
- The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Usage Data Collection

- Continuous data collection on individual queries was supported by Rapporter®, a data analysis and reporting application for the use of the R® statistical software environment in the cloud.
- The number of queries on specific antibiotic templates by geolocalized IP address and anonymised parameters were collected and evaluated for CPU time.
- The frequency of successfully generated reports was also evaluated by comparing the number of queries generated with and without an error message.

Data Analysis and Graphics

- The R® software environment for statistical computing and graphics was used to generate the plots and calculate summary statistics of the data.

Figure 1. Graphical overview of the technology of ID - ODS™

RESULTS

IDODS visitors (n = 5678) all around the world

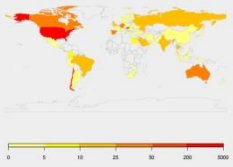


Figure 2. Cluster map of ID - ODS™ visitors from around the world

Template	% of all Utilization	Mean ± SD CPU Time (sec)	% Aborted
Piperacillin and Tazobactam PTA	15.90	5.40 ± 1.34	2.82
Empiric Vancomycin Dosing	15.10	4.90 ± 1.06	3.73
Bayes Aminoglycosides Optimization	15.50	9.00 ± 64.42	37.14
Bayes Vancomycin Optimization	7.90	18.30 ± 6.85	41.65
Cefepime PTA	14.10	6.50 ± 3.32	4.23
Meropenem PTA	8.70	10.70 ± 3.05	1.87
Other	22.80	6.00 ± 1.18	11.91

Table 1. Summary statistics of select ID - ODS™ template utilization

CONCLUSION

- The availability of this cross-platform application provides the foundations for a multi-model based, point of care clinical decision support tool on desktops and mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system has been used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation over 5000 times since implementation.
- Subsequent development will focus on improving the user interface in order to attempt to minimize the rate of inaccurate data entry into ID - ODS™, the web - based clinical decision support tool used to individualize antimicrobial therapy.

REFERENCES

1. Garritty et al. J Med Internet Res. 2006, 8(2):e7.
2. Mosa et al. BMC Med Inform Decis Mak. 2012, 12:67
3. http://hopkins-abxguide.org
4. http://www.sanfordguide.com
5. Burdette et al. CID 2008, 47: 117-122
6. http://www.R-project.org
7. http://rapporter.net
8. www.optimum-dosing-strategies.org

Contact: Andras Farkas, Pharm.D, Director of Computer Simulation Studies, Optimum Dosing Strategies, Bloomingdale, NJ, info@optimum-dosing-strategies.org Tel: (845) - 800 - 9911

EV0004

Development of a Smart Phone application to individualize antibiotic dosing in critically ill patients using Monte Carlo simulations, Bayesian feedback and drug interaction modeling approaches

Andras Farkas, Pharm.D[1]; Gergely Daroczi, PhDC[2]

Optimum Dosing Strategies, Bloomingdale, NJ[1] ; Easy Stats LTD, London, UK[2]

ABSTRACT/REVISED

Objectives: Smart phone technology can help facilitate mobile computing at the point of care. The objective of this study was to develop a mobile phone application to provide individual dosing recommendations based on Cumulative Fraction of Response (CFR), Probabilities of Target Attainment (PTA), Bayesian feedback and combination drug interaction modeling for several antibiotics. Here the example of Cefepime (CEF) is presented.
Methods: Population pharmacokinetic (popPK) model for CEF in critically ill patients is used as the Bayesian prior and to estimate concentration - time profiles for 5000 virtual patients per simulation. Additionally, the Greco interaction equation is employed and linked to simulated concentration - time profiles to generate the curve of killing effect for combination therapy. The models and conditions are coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) on - line to provide the necessary background for the high - level computations.
Results: The user provides patient demographic and laboratory information (including institution specific MIC distribution) via a user friendly interface in conventional units, which is then passed through the template of conditions in ID-ODSTM. PTAs for short, extended, or continuous infusion regimens for the target fT>MIC of 60% for MICs up to 32 µg/ml in serum are established assuming lognormal distribution for all pharmacokinetic parameters. These PTAs are also used to calculate CFRs, allowing to compare up to 4 different regimens side by side at a time. For Bayesian dose individualization, a total of 5000 iterations are completed using a sequential approach allowing for the change of PK parameters from time to time. After the computation, clinically useful information including individual PK parameter estimates and suggested dosing regimens, PTAs, CFRs, and the predicted killing effect of the candidate dosing strategies will be displayed using uncomplicated and adequately descriptive plotting designs.
Conclusions: This mobile-platform application provides the opportunity for clinicians interested in optimizing antimicrobial therapy at the point of care. This system can be used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach, Bayesian feedback and Monte Carlo simulation.

INTRODUCTION

- In the past several years, adaptation of the use of on-line applications on mobile devices by health care professionals has become increasingly more common. [1,2]
- Tablets, iPad®s and smartphones are mobile technologies that combine telecommunications and data processing in a devices that can facilitate computing at the point of care.
- Drug reference resources generally provide information on the pharmacology, dosing, dosage form, drug interactions and the contraindications associated with the use of the agents.
- Popular and trusted resources like The John Hopkins Antibiotic Guide and the Sanford Guide both have been available for many years now, with sections focusing on the dosing of antibiotics[3,4]. Neither of these two resources directly provide drug dosing information based on the results of high quality popPK models.
- They also do not provide the opportunity to evaluate different dosage regimens for probabilities of target attainment based on Monte Carlo simulation. As on-line computing and the use of mobile devices become more and more popular, transition of the free-standing software to a web – based application is likely inevitable. Virtually all available devices have the option to view websites, with some having significantly better aesthetic appearance compared to others[5].
- In this experiment, we report on the enhancement of a multi-platform, web-based clinical application equipped to provide optimum antibiotic dosing information via the use of population pharmacokinetic models and Bayesian adaptive feedback or Monte Carlo simulation and drug interaction modeling for critically ill patients at the point of care.

METHODS

ID – ODS™ Technology Overview [6,7,8]

- Using any of the popular devices and browsers [1] all parameters passed to Optimum Dosing Strategies (ODS) website [2] are seamlessly transmitted to Rapporter servers over a secure channel for evaluation.
- The channel is backed up by a content delivery network [3] that is also speeding up connection as well as making it possible to provide high availability for ODS users.
- The cluster of webservers [4] process the queries and read the required models and programs to memory from the distributed system of databases [5] to be passed along to the R [6] workers.
- The computations are run in a secured and stateless R environment so that no sensitive information would be stored for future R sessions. The statistical tasks will use any of the numerous, user contributed packages found on CRAN like the FME package as a Bayesian interface.
- The results are returned in Pandoc's markdown format [8] that could be transformed to any popular document format – along with the generated plots in the analysis.

Data Analysis and Graphics

- The R® software environment for statistical computing and graphics was used to generate the plots and calculate summary statistics of the data.
- Respective R® software packages are used to support computations related to Monte Carlo simulation, Bayesian analysis and drug interaction modeling.

Figure 1. Graphical overview of the technology of ID - ODS™

RESULTS

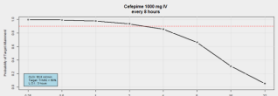


Figure 2. Output of the Monte Carlo simulation based optimization application

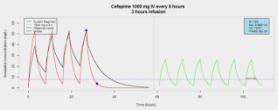


Figure 3. Output of the Bayesian feedback driven dose optimization application

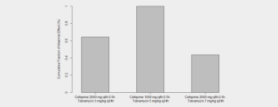


Figure 4. Output of the drug interaction simulation based application

CONCLUSION

- The availability of this cross-platform application provides a multi-model based, point of care clinical decision support tool on desktops and mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system has been used to improve antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacodynamics, popPK model based approach and Monte Carlo simulation over 5000 times since implementation.
- Current updates in the development of this application enable practitioners to utilize Bayesian feedback driven dose optimization at the bedside. In addition, the availability of drug interaction simulation option allows for the evaluation of the cumulative fraction of maximum effect for different combination therapy regimens aimed to maximize killing effect throughout the course of treatment.

REFERENCES

1. Garritty et al. J Med Internet Res. 2006, 8(2):e7.
2. Mosa et al. BMC Med Inform Decis Mak. 2012, 12:67
3. http://hopkins-abxguide.org
4. http://www.sanfordguide.com
5. Burdette et al. CID 2008, 47: 117-122
6. http://www.R-project.org
7. http://rapporter.net
8. www.optimum-dosing-strategies.org

Contact: Andras Farkas, Pharm.D, Director of Computer Simulation Studies, Optimum Dosing Strategies, Bloomingdale, NJ, info@optimum-dosing-strategies.org Tel: (845) - 800 - 9911

Development of an on-line application to support a program aimed to evaluate antimicrobial dosing optimization without therapeutic drug monitoring in critically ill patients in Brazil

Samuel Duttra[1]; Cristina Sanches Giraud[1]; Jason A. Roberts, PhD, FSHP[2]; Gergely Daroczi, PhD(c)[3]; Kimberly Sarosky, Pharm.D, BCPS[4]; Andras Farkas, Pharm.D[5]

Federal University of Sao Joao del Rey, Divinópolis/, Brazil[1]; Burns Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia[2]; EasyStats LTD, London, UK[3]; Mount Sinai St. Luke's Hospital, NY, NY[4]; Optimum Dosing Strategies, Bloomingdale, NJ[5]

ABSTRACT

Background: Enhancing the quality of prescribing and administration of antibiotics should be considered a key priority for improving therapeutic outcomes and suppressing the increasing rates of resistance that is presently observed worldwide. The availability of therapeutic drug monitoring (TDM) for many of the commonly used antibiotics is a rarity in a considerable number of centers around the world. Alternatively, the use of a widely available web based application utilizing population PK models and sophisticated simulation algorithms may have the potential to be a valuable tool in optimizing PKPD indices. The aim of this study was to describe the process of modifying an on-line dose optimization application to meet the needs of a program designed to evaluate the adaptation of published population PK models for dose optimization in the absence of TDM into the care of Brazilian critically ill patients.

Materials/methods: Piperacillin and tazobactam PK models are coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) on - line using the R language to provide the necessary background for the high - level computations to estimate concentration - time profiles for 5000 virtual patients per simulation. The user provides patient demographic and laboratory information (including MICs) via a user friendly html interface in international units. PTAs for up to 200 short and extended infusion regimens from 2000 to 8000 mg of piperacillin at 50 mg intervals given every 12, 8, 6 and 4 hours for the target ƒT>MIC of 50% for MICs up to 32 μg/ml in serum are established assuming 70% protein binding and lognormal distribution for all pharmacokinetic parameters.

Results: PTAs for all simulated regimens are evaluated and a subset reaching 90% or more is separated for further analysis to provide the dosing regimen that achieves the optimal target at the pre-specified MIC with the least amount of drug in mgs to be administered in a 24 h time period. Once computation is accomplished, clinically relevant information including patient demographics, suggested dosing regimens, PTAs, and creatinine clearance will be displayed using uncomplicated and adequately descriptive plotting designs and in the Portuguese language (Figure 1. and 2.).

Conclusion: The development of this modified application provides the foundations for a multi-model based, point of care clinical decision support tool on the web and mobile devices for clinicians focusing on optimizing antimicrobial therapy. In the absence of available and affordable TDM, this system will be used to evaluate the adaptation of published population PK models for dose optimization into the care of the Brazilian critically ill patients. By setting the application to give the dosing regimen that uses the lowest amount of drug per day, the cost will also be kept to the minimum necessary to provide optimal exposure.

INTRODUCTION

- In the past several years, adaptation of the use of on-line applications on mobile devices by health care professionals has become increasingly more common.[1,2]
- Tablets, iPad®s and smartphones are mobile technologies that combine telecommunications and data processing in a devices that can facilitate computing at the point of care.
- ID – ODS™ is a TDM and simulation tool powered by the R® software with an extensive model library built from population pharmacokinetic models published in peer reviewed literature. Based on patient demographic information readily available at the bedside, ID – ODS™ incorporates Monte Carlo simulation and inverse Bayesian modeling into the design of personalized dosing regimens via a graphical user interface.[3]
- In this report we describe the process of modifying the on-line dose optimization application ID – ODS™ to meet the needs of a program designed to evaluate the implementation of published population PK models for dose optimization in the absence of TDM into the care of critically ill patients in Brazil.

METHODS

- Piperacillin and tazobactam PK models are coded into Individually Designed Optimum Dosing Strategies (ID-ODS™) on – line, where the user provides patient demographic and laboratory information (including MICs) via a user friendly html interface in Portuguese and in international units.
- Using any of the popular devices and browsers all parameters passed to Optimum Dosing Strategies (ODS) website are seamlessly transmitted to Rapporter servers over a secure channel for evaluation.[4]
- The cluster of webservers process the queries and read the required models and programs to memory from the distributed system of databases to be passed along to the R® workers.[5]
- PTAs for short and extended infusion regimens from 2000 to 8000 mg of piperacillin at 50 mg intervals given every 12, 8, 6 and 4 hours for the target ƒT>MIC of 50% for MICs up to 32 μg/ml in serum are established assuming 30% protein binding.
- Subsequently, all simulated regimens are evaluated and a subset reaching 90% or more is identified for further analysis to provide the regimen that achieves the optimal target at the pre-specified MIC with the least amount of drug in mgs to be administered in a 24 h time period.
- The results are returned in Pandoc's markdown format that could be transformed to any popular document format – along with the generated plots in the analysis.

Data Analysis and Graphics

- The R® software environment for statistical computing and graphics is used to generate the plots and calculate summary statistics of the data.
- Respective R® software packages are used to support computations related to Monte Carlo simulation

Figure 1. Graphical overview of the technology of ID - ODS™

RESULTS

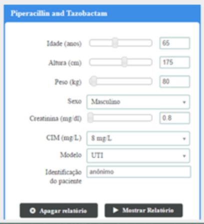


Figure 2. Graphical User Interface of ID-ODS™ for Monte Carlo simulation translated in Portuguese

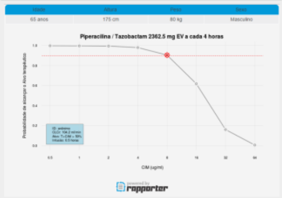


Figure 3. Output of the Monte Carlo simulation based optimization in Portuguese

CONCLUSION

- The availability of this cross-platform application provides a multi-model based, point of care clinical decision support tool on desktops and mobile devices for clinicians interested in optimizing anti-infective therapy.
- This system has been used to facilitate the optimization of antibiotic dosing practices at the bedside via the utilization of modern principles of antimicrobial pharmacokinetics and pharmacodynamics.
- Current updates in the development of this application enable Portuguese speaking practitioners to evaluate Monte Carlo simulation driven dose optimization at the bedside.
- In the near future, the clinical utility of the application in a resource limited setting will be evaluated by comparing predicted and observed PKPD index target attainment to establish the viability of model based dose optimization without therapeutic drug monitoring for antimicrobial agents.

REFERENCES

1. Garritty et al. J Med Internet Res. 2006, 8(2):e7.
2. Mosa et al. BMC Med Inform Decis Mak. 2012, 12:67
3. www.optimum-dosing-strategies.org
4. http://rapporter.net
5. http://www.R-project.org

Contact Andras Farkas, Pharm.D, Director of Computer Simulation Studies, Optimum Dosing Strategies, Bloomingdale, NJ; farkasa@optimum-dosing-strategies.org Tel (845) - 800 - 9911

A - 1318

Comparative Evaluation of the Performance of a Population Equation and Two Bayesian Methods to Predict Future Vancomycin Concentrations

Andras Farkas, Pharm.D[1]; Sarith Saju, Pharm.D. Candidate[2]; Patrick Galdun, Pharm.D. Candidate[2]; Phillip Villasurda, Pharm.D. Candidate[3]; Jason A. Roberts, PhD[4,5]

Optimum Dosing Strategies, Bloomingdale, NJ[1]; University of Buffalo, School of Pharmacy, Buffalo, NY[2], Touro College of Pharmacy, New York, NY[3], Royal Brisbane and Women's Hospital, Brisbane, Australia[4]; Burns, Trauma and Critical Care Research Centre, The University of Queensland, Brisbane, Australia[5]

ABSTRACT

Objectives: Vancomycin (VAN) therapeutic drug monitoring (TDM) with Bayesian feedback has been studied before, but there are few reports of the accuracy and precision of predictions when fitting concentrations via the parametric method from dose to dose (sequential) compared with the method where fitting all concentrations takes place at once (fixed). The goal of this study was to compare the performance of Bayesian methods and the published Matzke equation without feedback at predicting future VAN concentrations.

Methods: VAN concentrations were collected from a mixed population as part of a clinical TDM program. The Matzke equation was coded into Individually Designed Optimum Dosing Strategies (ID-ODSTM) online and used as the Bayesian prior. Up to five observed levels were predicted per patient. The mean prediction error (ME) and mean squared prediction error (MSE) and their 95% confidence intervals (95%CI) were calculated to measure absolute bias and precision, while delta ME (Δ ME) and delta MSE (Δ MSE) and their 95% CI to measure relative bias and precision, respectively.

Results: 695 VAN levels from 171 patients were analyzed. MEs (95%CI) ranged from 2.18 (0.87, 3.5) to 3.08 (1.56, 4.6) for the Matzke equation, 0.068 (-1.05, 1.19) to 1.32 (0.01, 2.64) for the fixed and -0.89 (-2.39, 0.61) to 0.94 (-0.42, 2.31) for the sequential approach, indicating a consistently non-significant difference in bias for the sequential method. MSEs (95%CI) ranged from 64.78 (48.09, 81.48) to 80.15 (48.44, 111.86) for Matzke, 41.98 (27.74, 56.22) to 54.27 (37.49 to 71.05) for the fixed, and 38.81 (23.6, 54.02) to 57.79 (37.17, 78.41) for the sequential approach. When compared relative to the Matzke method, the sequential approach showed lower Δ MEs and Δ MSEs versus the fixed method with Δ ME (95%CI) values of -3.73 (-5.21, -2.24) to -1.88 (-3.54, -0.22) and -2.30 (-3.67, -0.94) to -1.50 (-3.04, 0.04), respectively.

Conclusion: The predictive performance of the sequential method was shown to be superior over the fixed approach, which in turn suggests that it should be preferred for use in a clinical TDM program.

INTRODUCTION

- Therapeutic drug monitoring (TDM) is suggested for vancomycin (VAN) to achieve timely and therapeutic concentrations.[1]
- A variety of dosing methods are used for VAN because of a difficult-to-predict relationship between dose and serum concentrations.[2]
- For serum concentration data, the Bayesian approach appears to give the best predictive performance.[3,4,5]
- The goal of this study was to compare the performance of Bayesian methods and the published Matzke equation without feedback at predicting future VAN concentrations.

METHODS

- TDM data was collected retrospectively from 171 patients receiving VAN therapy via short and continuous infusion.
- The ID – ODS™ program was used to predict VAN concentrations using a one compartment intravenous infusion model.
- The FME package was utilized to carry out the Bayesian analysis via the Markov Chain Monte Carlo technique using the Metropolis – Hastings algorithm.[6]
- Analysis of prediction errors was based on calculated mean (ME) and delta mean prediction errors (ΔME) and mean squared (MSE) and delta mean squared prediction errors (ΔMSE) using the R® software.[6]

RESULTS

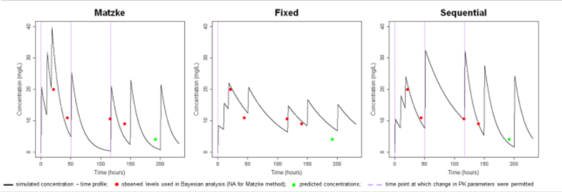


Figure 1. Simulated concentration – time profiles for Patient #37 by respective methods

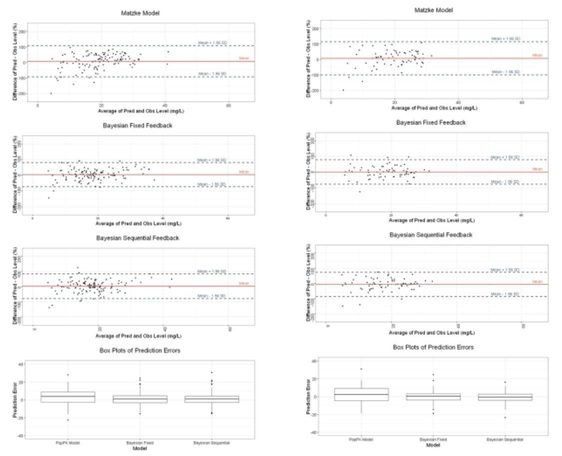


Figure 2. Bland – Altman percent difference plots and box plots of prediction errors for the 3rd (left column) and 5th (right column) observed versus predicted concentrations

RESULTS

Model	BIAS AND PRECISION VS OBSERVED LEVELS			
	Mean	95% CI	Mean	95% CI
	ME - 2nd level		MSE – 2nd level	
Matzke	2.18	0.87 to 3.50	64.78	48.09 to 81.48
Bayesian	0.068	-1.05 to 1.19	43.97	32.07 to 55.87
	ME - 3rd level		MSE - 3rd level	
Matzke	2.82	1.29 to 4.36	79.43	58.67 to 100.20
Fixed	1.32	0.01 to 2.64	54.27	37.49 to 71.05
Sequential	0.94	-0.42 to 2.31	57.79	37.17 to 78.41
	ME - 4th level		MSE - 4th level	
Matzke	3.08	1.56 to 4.60	67.41	48.43 to 86.38
Fixed	0.77	-0.50 to 2.06	41.98	27.74 to 56.22
Sequential	-0.64	-1.88 to 0.58	38.81	23.60 to 54.02
	ME - 5th level		MSE - 5th level	
Matzke	2.16	0.06 to 4.46	80.15	48.44 to 111.86
Fixed	0.21	-1.47 to 1.90	48.71	25.60 to 71.82
Sequential	-0.89	-2.39 to 0.61	39.45	19.94 to 58.95
ME – Mean Prediction Error, MSE – Mean Squared Prediction Error				

Table 1. Bias and precision of the methods evaluated versus the observed concentrations

Model	BIAS AND PRECISION RELATIVE TO MATZKE MODEL					
	Mean	95% CI	Rank	Mean	95% CI	Rank
	Δ ME - 2nd level			Δ MSE - 2nd level		
Bayesian	-2.11	-3.33 to -0.89	N/A	-20.81	-38.19 to -3.43	N/A
	Δ ME - 3rd level			Δ MSE - 3rd level		
Fixed	-1.50	-3.04 to 0.04	2	-25.16	-50.70 to 0.38	1
Sequential	-1.88	-3.54 to -0.22	1	-21.64	-51.02 to 7.73	2
	Δ ME - 4th level			Δ MSE - 4th level		
Fixed	-2.30	-3.67 to -0.94	2	-25.42	-45.37 to -5.48	2
Sequential	-3.73	-5.21 to -2.24	1	-28.58	-48.3 to -8.88	1
	Δ ME- 5th level			Δ MSE - 5th level		
Fixed	-1.94	-3.37 to -0.52	2	-31.43	-53.03 to -9.84	2
Sequential	-3.06	-4.67 to -1.45	1	-40.69	-74.64 to -6.74	1
ME – Mean Prediction Error, MSE – Mean Squared Prediction Error						

Table 2. Bias and precision of the Bayesian methods relative to the Matzke model without feedback

CONCLUSION

- Our results suggest that Bayesian simulations with feedback are more accurate at predicting future VAN concentrations than traditional non-feedback methods.
- Based on the performance displayed by the sequential method it would be sensible to utilize it in a TDM program over a fixed approach in an effort to obtain therapeutic concentrations at higher accuracy and better precision.
- The relatively low over all predictive performance of these methods warrants further studies to be completed aimed to identify additional factors that may explain inter - patient variability and better define PK parameters and hence improve the usefulness of this methods.

REFERENCES

1. Rybak M. et al. Am J Health Syst Pharm 2009; 66:82–98.
2. Bulitta J. et al. Curr Pharm Biotechnol. 2011;12(12):2044–2061.
3. Hiraki Y. et al. J Clin Pharm Ther. 2010;35(5):527–32.
4. Hurst A. Antimicrob Agents. 1990;34(6).
5. Llopis-Salvia P. J Clin Pharm Ther. 2006;31(5):447–54.
6. http://www.R-project.org

Contact Andras Farkas, Pharm.D, Director of Computer Simulation Studies, Optimum Dosing Strategies, Bloomingdale, NJ; motyocska@yahoo.com, Tel: (845) - 800 - 9911

#292

Evaluation of Pharmacist Managed Vancomycin Therapy Compared to Physician Managed Dosing in Establishing Timely and Therapeutic Vancomycin Serum Concentrations at a Community Hospital

Rachel Sussman, Pharm.D[1]; Andras Farkas, Pharm.D[1,2]; Andrea Lee Pharm.D Candidate[3]
Nyack Hospital, Nyack, NY[1]; Optimum Dosing Strategies, Teaneck, NJ[2]; Touro College of Pharmacy New York, NY[3]

Andras Farkas, Pharm.D
Director, CCPKPD
Nyack Hospital, Nyack, NY
farkasa@nyackhospital.org
Tel: (845) - 348 -2606

ABSTRACT

Purpose: Vancomycin (VAN) remains a mainstay for the treatment of serious infections caused by gram-positive organisms. The purpose of this study was to assess if pharmacist managed therapy can produce timely therapeutic levels at least as effectively as physician managed dosing of VAN.

Methods: A total of 100 patients per group were evaluated for baseline characteristics. Demographic, laboratory and VAN monitoring data were collected. Percentage of patients with initial, second, and third levels within subtherapeutic (<10 mg/L), therapeutic (10 to 20 mg/L) and supratherapeutic (>20 mg/L) ranges were compared. Secondary end points included comparing initial mean ± SD VAN concentrations, levels between 8 and 22 mg/L, percentage of patients never reaching concentrations of ≥10 mg/L, and time to reach the therapeutic range.

Results: There were no statistically significant differences in baseline characteristics between the two groups evaluated, except for baseline renal function. VAN levels within the therapeutic range for initial, second and third measurements were 77%, 71%, 74% for pharmacist managed therapy and 37%, 58%, 55% for the comparator. Initial mean ± SD VAN levels were 13.4 ± 3.6 mg/L and 8.8 ± 3.9 mg/L ($p < 0.05$), while levels between 8 and 22 mg/L were 88% and 63%, for the intervention and comparator groups, respectively. An additional 40% of patients never reached 10 mg/L in the physician group compared to the intervention group. Median ± SD number of days to reach therapeutic range was 1.9 ± 0.9 days for the intervention group versus 2.5 ± 2.7 days for the comparator group ($p < 0.05$).

Conclusion: Pharmacist managed VAN therapy resulted in both a greater percentage of therapeutic levels and a shorter time to reach therapeutic range. Consequently, the pharmacist managed VAN therapy appears to be at least as or more effective in achieving pre-specified laboratory endpoints when compared to physician dosing of VAN at our institution.

INTRODUCTION

VAN remains a mainstay for the treatment of serious infections caused by gram-positive organisms. VAN is a glycopeptide antibiotic with linear pharmacokinetics and specified therapeutic levels recommended by the Infectious Disease Society of America (IDSA) based upon indication.[1] In order to attain pre-specified therapeutic VAN levels there are several nomograms developed to aid in the empiric dosing of VAN.[1,2,3] Dosing based on established nomograms can result in a higher percentage of patients with serum levels within these specified therapeutic ranges.[2,3] For instance, Kullar, et al validated the effectiveness of a VAN nomogram in achieving trough concentrations of 15-20 mg/L; the nomogram resulted in 80% of the VAN trough levels between 13-22 mg/L.[2] Leu et al, also concluded that 65% of patients had a VAN trough of 10-15mg/L when dosed with a nomogram compared to 32% with conventional dosing. Additionally, the patients dosed by the nomogram had better clinical outcomes (higher rate of cure and eradication) and an improved safety profile.[3] Thus, a protocol was established at our institution based on published adult population equations to calculate initial dose and make further dose adjustments based on measured VAN serum levels. Then, a team of staff and clinical pharmacists was assembled to develop a publicly available on-line application to support effortless and safe implementation of the VAN dosing services[4]. Finally, the procedure for work flow to provide 24 hours 7 days a week coverage was established. The purpose of this study was to assess if pharmacist managed therapy can produce timely therapeutic levels at least as effectively as physician managed dosing of VAN.

METHODS

- Pharmacist managed VAN at our institution include pharmacists calculating initial dosing regimens, determining timing of serum VAN level draws, and dose adjustments based on the levels drawn

- The calculation for VAN dosing is available as a dosing calculator at *http://optimum-dosing-strategies.org* and also as an application for personal electronic devices as shown below:

- Pharmacist managed VAN therapy was then compared to conventional physician managed VAN dosing at our institution
- Inclusion criteria included patients who were over 18 years of age, had a presumed infection, and had at least one measured VAN serum level
- A total of 100 patients per group were evaluated for baseline characteristics such as, demographic, laboratory and VAN monitoring data
- Primary endpoints included: percentage of patients with initial, second and third levels within subtherapeutic (<10 mg/L), therapeutic (10 to 20 mg/L) and supratherapeutic (>20 mg/L) ranges
- Secondary endpoints included: Initial mean ± SD VAN concentrations; levels between 8 and 22 mg/L; percentage of patients never reaching concentrations of ≥10 mg/L, and time to reach the therapeutic range.
- Normality was assessed with the Shapiro-Wilk test, categorical variables were then compared using the Mann-Whitney U test and continuous variables were compared using the student t-test utilizing the R Software.[5]

RESULTS

Table 1. Baseline Demographics

	Physician Managed (N=100)	Pharmacy Managed (N=100)	P-value
Mean Age (years)	70	67	0.20
Mean Height (inches)	66	66	0.98
Mean creatinine (mg/dl)	1.3	1.0	0.02
Gender (% male)	50	64	1.00
ICU patients(%)	10	10	0.42

Chart 1. Percentage of therapeutic VAN levels

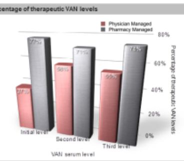


Chart 2. Initial VAN levels

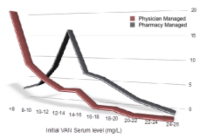
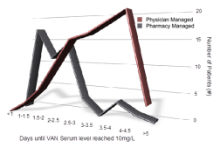


Chart 3. Time to reach a VAN level of ≥10 mg/L



RESULTS

Chart 4. Days to reach level of ≥10mg/L

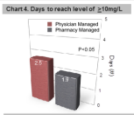


Chart 5. Initial Mean VAN levels

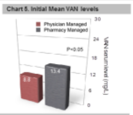


Table 2. Distribution of second VAN levels

	Physician Managed Percentage of VAN levels(%)	Pharmacy Managed Percentage of VAN levels(%)
VAN level 10-20 mg/L	58	71
VAN level <8 mg/L	22	0
VAN level 8-22 mg/L	62	89
VAN level 22-25 mg/L	12	9
VAN level 25-30 mg/L	0	2
VAN level >30 mg/L	4	0

Table 3. Distribution of third VAN levels

	Physician Managed Percentage of VAN levels(%)	Pharmacy Managed Percentage of VAN levels(%)
VAN level 10-20 mg/L	55	74
VAN level <8 mg/L	0	0
VAN level 8-22 mg/L	81	90
VAN level 22-25 mg/L	3	10
VAN level 25-30 mg/L	16	0
VAN level >30 mg/L	0	0

Table 4. Percentage of patients never reaching a level of ≥10mg/L

Physician Managed	Pharmacy Managed	P-value
40	0	<0.001

CONCLUSION

- Pharmacy managed VAN therapy resulted in a greater percentage of patients with therapeutic levels. For example, VAN levels within the therapeutic range for initial, second and third measurements were 77%, 71%, 74% for pharmacist managed therapy and 37%, 58%, 55% for the physician managed therapy.
- Pharmacy managed VAN therapy resulted in a shorter time to reach the pre-specified therapeutic range, as median ± SD number of days to reach therapeutic range was 1.9 ± 0.9 days for the intervention group versus 2.5 ± 2.7 days for the comparator group ($p < 0.05$).
- Pharmacy managed VAN therapy appears to be at least as or more effective in achieving pre-specified therapeutic serum levels when compared to physician dosing of VAN at our institution.

REFERENCES

1. Aubron C, Corallo C, Nunn M et al. Evaluation of the Accuracy of a Pharmacokinetic Dosing Program in Predicting Serum Vancomycin Concentrations in Critically Ill Patients. An Pharmacother 2011; 45:1193-8. 1
2. Kullar R, Leonard S, Davis S et al. Validation of the Effectiveness of a Vancomycin Nomogram in Achieving Target Trough Concentrations of 15-20mg/L Suggested by the Vancomycin Consensus Guidelines. Pharmacotherapy 2011; 31(5):441-448.2
3. Leu WJ, YC Liu, HW Wang et al. Evaluation of a vancomycin dosing nomogram in achieving high target trough concentrations in Taiwanese patients. Int J Infect Dis. 2012 Aug 20.3
4. Optimum Dosing Strategies. Teaneck, NJ. Available from: http://optimum-dosing-strategies.org/
5. R. Version 2.15.2012-06-11. isbn 3-900051-08-9.